USE OF ADVISORY COMMITTEES BY THE FOOD AND DRUG ADMINISTRATION

(PART 2)

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON

GOVERNMENT OPERATIONS

HOUSE OF REPRESENTATIVES

NINETY-FOURTH CONGRESS

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APPENDIX

USE OF ADVISORY COMMITTEES BY THE FOOD AND DRUG ADMINISTRATION
(Part 2)

WEDNESDAY, APRIL 23, 1975

HOUSE OF REPRESENTATIVES,
INTERGOVERNMENTAL RELATIONS
AND HUMAN RESOURCES SUBCOMMITTEE
OF THE COMMITTEE ON GOVERNMENT OPERATIONS,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2247, Rayburn House Office Building, Hon. L. H. Fountain (chairman of the subcommittee) presiding.

Present: Representatives L. H. Fountain, Don Fuqua, Robert F. Drinan, Glenn English, Elliott H. Levitas, and John W. Wydler.

Also present: Delphis C. Goldberg, professional staff member; Gilbert S. Goldhammer, consultant; and Richard L. Thompson, minority professional staff, Committee on Government Operations.

Mr. FOUNTAIN. The subcommittee will come to order.

The record will show a quorum is present for the purpose of taking testimony.

This hearing is intended to complete the record developed in hearings held during March, April, and May of last year on FDA's use of advisory committees and FDA's compliance with the requirements of the Federal Advisory Committee Act. This will probably be the final subcommittee hearing on this subject prior to completion of a report now in preparation. The subcommittee's investigation and hearings have disclosed a number of serious deficiencies which will be fully discussed in the report. However, I am pleased to say that the agency has acknowledged some of these deficiencies and has taken steps to correct them.

Last year the subcommittee examined the role of advisory committees in FDA actions concerning a number of drugs, including propranolol for angina pectoris, Depo Provera as an injectable contraceptive, and DES as a "morning after" contraceptive. These subcommittee hearings, and our related oversight activities, have resulted in regulatory actions that should significantly enhance the public's health protection.

We plan now to examine the role of several advisory review panels in evaluating over-the-counter drugs, specifically the work of the OTC antacid and antiperspirant review panels, and, if time permits, the antimicrobial panel. We will also examine recent advisory committee deliberations on the safety of the Dalkon shield, an intrauterine contraceptive device, that was discussed in subcommittee hearings held in May and June 1973.

While I recognize that FDA has previously testified before Senate committees on some of these matters, our inquiry relates to different aspects and is based upon new information with respect to the drugs and panels concerned. We will avoid unnecessary duplication.

Our witnesses include those FDA officials who are most familiar with the functioning of the advisory panels involved in this hearing.

We will begin with an examination of the advisory role of the antiperspirant review panel, with special emphasis on its review of aerosol spray antiperspirant preparations containing zirconium compounds.

We have with us today Alexander M. Schmidt, M.D., Commissioner of Food and Drugs, Food and Drug Administration; J. Richard Crout, M.D., Director, Bureau of Drugs; Mr. Peter B. Hutt, Chief Counsel; Mr. Robert C. Wetherell, Jr., Director, Office of Legislative Services; Mr. Robert G. Pinco, Chief, Division of OTC Evaluation; Dr. John Jennings, Associate Commissioner for Medical Affairs; and Mr. David M. Link, Acting Director, Bureau of Medical Devices and Diagnostic Products.

We want to welcome you and your colleagues, Dr. Schmidt; we appreciate your presence and your willingness to cooperate in the hearings.

I understand that you have a brief statement you would like to make preparatory to questioning.

You may proceed at this point.

STATEMENT OF ALEXANDER M. SCHMIDT, M.D., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE; ACCOMPANIED BY J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS; PETER BARTON HUTT, CHIEF COUNSEL; ROBERT C. WETHERELL, JR., DIRECTOR, OFFICE OF LEGISLATIVE SERVICES; ROBERT G. PINCO, CHIEF, DIVISION OF OTC EVALUATION; JOHN JENNINGS, M.D., ASSOCIATE COMMISSIONER FOR MEDICAL AFFAIRS; AND DAVID M. LINK, ACTING DIRECTOR, BUREAU OF MEDICAL DEVICES AND DIAGNOSTIC PRODUCTS

Dr. SCHMIDT. Thank you, Mr. Chairman. I also have with me Mr. Robert Pinco, Chief, Division of OTC Evaluation.

Mr. FOUNTAIN. Nice to have you with us.

Dr. SCHMIDT. Behind me are Dr. John Jennings and Mr. David Link, Director of the Bureau of Medical Devices. If necessary they can contribute to our session this morning.

I did want to make just two or three points which I think are important in a brief statement.

We are pleased to be here this morning and believe this is an important subject.

I understand from your letter of invitation that today's inquiry will turn to the review we are conducting of over-the-counter drugs, and the role played therein of advisory committees, or, as they are known in this case, OTC panels.

To me, this is an excellent area for discussion, as the role of advisory committees in the OTC review typifies what I think to be the most positive aspects of the use of advisory committees by a Federal agency.

First, through the use of the OTC panels, FDA and the American people benefit in a number of important ways. Perhaps most important is the trust in the entire OTC review process that has been engendered by our use of advisory panels, operating in an open fashion. Through the process we have established, the public and the industry can observe and participate in the review and evaluation. In a real sense, the OTC review is not a Federal agency dictating, ex cathedra, how the American public and the American industry must behave. Instead, we have found a way to work together that engenders trust in the process and in the outcome, through involvement by the concerned parties, including the public. This enables the agency to take definitive action on the basis of the panel reports with a minimum of challenge on nonsubstantive issues, and a minimum of very costly, time-consuming, legal challenges.

We have now had enough experience with the OTC review to know that it is sound and is working very well, indeed.

Second, we have evolved a process that enables us to tackle a herculean job in a practical period of time. Two aspects of the OTC review would have given the agency, acting alone, much trouble: the immensity of the task—hundreds of thousands of products to review and evaluate, and the great variety of products, calling for a tremendous range of expertise. We have been able to call on literally scores of experts from across the country who in turn have called on dozens of other experts from around the world, who, among them all, have been exceptionally knowledgeable in the many subject areas of the review.

Third, the educational value of the process has been incalculable. The OTC review has been an open national forum, allowing many people to come and see us, see what we do, see how we do it, and why. They have helped us, made suggestions for our improvement, told others and the general public about us, about our work, and about OTC drugs. Just the newspaper coverage of the problems uncovered by the review so far has educated many people to the fact that OTC drugs are drugs not candy. The regulatory monographs will, I believe, turn out to be of great and lasting value to all parts of the health care system, from drug manufacturers to medical and nursing students learning about rational self-therapy.

Lastly, the output of the OTC panels becomes the input to the FDA, so that in the last analysis, no agency authority or responsibility is abridged. I am ultimately responsible for everything that happens, and in this case, I bear that responsibility with a great amount of equanimity, because of the excellence of the panels.

So, in short, we are happy to discuss a very sound process that has been working well, and which, to my mind, illustrates the best of the advisory committee process, working well with our agency staff.

Mr. FOUNTAIN. Thank you very much, Dr. Schmidt. As has been our usual procedure, when a question is asked, if it happens to fall within the province of one of your assistants, do not hesitate to designate that person to answer the question.

The first topic to be considered is the work of FDA's antiperspirant advisory review panel. The reason we have chosen to look at this particular panel is that both FDA and the panel have had under consideration for some time questions concerning the safety of several

nationally advertised underarm antiperspirant aerosol sprays containing the chemical, zirconium.

I believe the principal products of this type currently on the market are Sure and Secret. Is this correct?

Dr. SCHMIDT. Yes.

Mr. FOUNTAIN. These deodorants are apparently widely used by the adult and, perhaps, also by the teenage population. The safety of their long-term use now appears to be in doubt. If that is so, it is imperative that these safety questions be resolved promptly. I want to stress that it is not the intention of this subcommittee to express any view at this time on the safety of these preparations. They may be entirely safe, or they may be harmful—we do not know. However, in our oversight role, we are obligated to get the facts necessary to determine whether or not FDA has taken appropriate action to protect the public health and to fulfill its obligations under the laws that it enforces. We are particularly interested in the nature and extent of the advisory panel participation in this matter.

We also need to know how FDA is using the panel's advice in discharging its regulatory obligations.

Before we get too deeply into the hearing, I want to explain that the background concerning FDA's regulation of zirconium antiperspirants of the aerosol spray type can be developed most comprehensively and effectively, in my opinion, by exploring the functioning of the FDA's antiperspirant panel in its consideration of the zirconium aerosols, as reflected in the minutes of the panel's meetings.

This will entail a chronological development of the facts and my reading into the record pertinent and significant portions of the minutes. However, I plan to intersperse this with questions intended to clarify points or make them more understandable to the subcommittee and the public, or to bring out the applicable requirements of the law.

I would, therefore, ask that the subcommittee members defer their questioning of the witnesses until a satisfactory background record has been developed. I believe that it may take about 20 minutes for me to do that.

In order that we may fully understand the role of the OTC antiperspirant review panel, Doctor, will you explain briefly FDA's purpose in creating this panel?

Dr. SCHMIDT. The purpose in creating the panel was simply to serve as a group of knowledgeable experts with a wide variety of experience and expertise to review the available literature on safety and efficacy of OTC products on the market, and based on their review to report to the Food and Drug Administration their reviews on the safety, efficacy, and proper conditions under which these products are used and can be used as OTC drugs safely.

The panel was further charged to render a report conveying their views fully and the reasons behind their views to the agency to be used as the basis for the evolution, then, of what I term a regulatory monograph. In brief that is the purpose of the panel.

Mr. FOUNTAIN. FDA's regulations relating to the establishment of this and other OTC drug review panels appear in title 21 of the Code of Federal Regulations, as revised June 1, 1974, at pages 231 through 236 of part 141 to part 599.

I am placing these pages, which are self-explanatory, into the record.

[The material referred to follows:]

CODE OF FEDERAL REGULATIONS—CHAPTER I—FOOD AND DRUG ADMINISTRATION

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

SUBPART A—GENERAL PROVISIONS

Sec.

SUBPART B—ADMINISTRATIVE PROCEDURES

AUTHORITY: Secs. 502, 503, 505, 601, 52 Stat. 1051, 1052, 1053, 1055, as amended (21 U.S.C. 352, 353, 355, 371) (5 U.S.C. 554), unless otherwise noted.

SOURCE: 39 FR 11741, Mar. 29, 1974, unless otherwise noted.

SUBPART A—GENERAL PROVISIONS

§ 330.1 General conditions for general recognition as safe, effective and not misbranded.

An over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and each of the conditions contained in any applicable monograph. Any product which fails to conform to each of the conditions contained in this part and in an applicable monograph is liable to regulatory action.

(a) The product is manufactured in compliance with current good manufacturing practices, as established by Part 133 of this chapter.

(b) The establishment(s) in which the drug product is manufactured is registered, and the drug product is listed, in compliance with Part 132 of this chapter. It is requested but not required that the number assigned to the product pursuant to Part 132 of this chapter appear on all drug labels and in all drug labeling. If this number is used, it shall be placed in the manner set forth in Part 132 of this chapter.

(c) The product is labeled in compliance with Chapter V of the act and § 1.100 et seq. of this chapter. For purposes of § 1.102a(b) of this chapter, the statement of identity of the product shall be the term or phrase used in the applicable monograph established in this part.

(d) The advertising for the product prescribes, recommends, or suggests its use only under the conditions stated in the labeling.

(e) The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 706 of the act and Parts 8 and 9 of this chapter.

(f) The product container and container components meet the requirements of § 133.9 of this chapter.

(g) The labeling contains the general warning: "Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a physician immediately." The Food and Drug Administration will grant an exemption from this general warning where appropriate upon petition.

(h) Where no maximum daily dosage limit for an active ingredient is established in this part, it is used in a product at a level that does not exceed the amount reasonably required to achieve its intended effect.

(i) The labeling for any drug for which an applicable monograph requires a drug interaction warning contains the following warning: "Warning: Do not take this product concurrently with a prescription drug except on the advice of a physician."

(j) It is recommended that the labeling of the product contain the quantitative amount of each active ingredient, expressed in terms of the dosage unit stated in the directions for use (e.g., tablet, teaspoonful).

§ 330.5 Drug categories.

Monographs promulgated pursuant to the provisions of this part shall be established in this Part 330 and following parts and shall cover the following designated categories:

(a) Antacids.
(b) Laxatives.
(c) Antidiarrheal products.
(d) Emetics.
(e) Antiemetics.
(f) Antiperspirants.
(g) Sunburn prevention and treatment products.
(h) Vitamin-mineral products.
(i) Antimicrobial products.
(j) Dandruff products.
(k) Oral hygiene aids.
(l) Hemorrhoidal products.
(m) Hematinics.
(n) Bronchodilator and antiasthmatic products.
(o) Analgesics.
(p) Sedatives and sleep aids.
(q) Stimulants.
(r) Antitussives.
(s) Allergy treatment products.
(t) Cold remedies.
(u) Antirheumatic products.
(v) Ophthalmic products.
(w) Contraceptive products.
(x) Miscellaneous dermatologic products.
(y) Dentifrices and dental products such as analgesics, antiseptics, etc.
(z) Miscellaneous (all other OTC drugs not falling within one of the above therapeutic categories.)

SUBPART B—ADMINISTRATIVE PROCEDURES

§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.

For purposes of classifying over-the-counter (OTC) drugs as drugs generally recognized among qualified experts as safe and effective for use and as not misbranded drugs, the following regulations shall apply:

(a) *Procedure for establishing OTC drug monographs*—(1) *Advisory review panels.* The Commissioner shall appoint advisory review panels of qualified experts to evaluate the safety and effectiveness of OTC drugs, to review OTC drug labeling, and to advise him on the promulgation of monographs establishing conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. A single advisory review panel shall be established for each designated category of OTC drugs and every OTC drug category will be considered by a panel. The members of a panel shall be qualified experts (appointed by the Commissioner) and may include persons from lists submitted by organizations representing professional, consumer, and industry interests. The Commissioner shall designate the chairman of each panel. Summary minutes of all meetings shall be made.

(2) *Request for data and views.* The Commissioner will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of OTC drugs. Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed monograph and the full report(s) of the panel. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the office of the Hearing Clerk of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of

those statutes. To be considered, eight copies of the data and/or views on any marketed drug within the class must be submitted, preferably bound, indexed, and on standard sized paper (approximately 8½ x 11 inches). When requested, abbreviated submissions should be sent. All submissions must be in the following format:

OTC Drug Review Information

I. Label(s) and all labeling (preferably mounted and filed with the other data—facsimile labeling is acceptable in lieu of actual container labeling).

II. A statement setting forth the quantities of active ingredients of the drug.

III. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

IV. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished drug product.

5. Pertinent medical and scientific literature.

V. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination of the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of the finished drug product.

5. Pertinent medical and scientific literature.

VI. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been

proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.

(3) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner with respect to the safety and effectiveness of the drugs in a designated category of OTC drugs. A panel may consult any individual or group. Any interested person may request an opportunity to present oral views to the panel; such request may be granted or denied by the panel. Such requests for oral presentations should be in written form including a summarization of the data to be presented to the panel. Any interested person may present written data and views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in paragraph (a)(2) of this section and within the time period established for the drug category in the notice for review by a panel.

(4) *Standards for safety, effectiveness, and labeling.* The advisory review panel, in reviewing the data submitted to it and preparing its conclusions and recommendations, and the Commissioner, in reviewing the conclusions and recommendations of the panel and the published proposed, tentative, and final monographs, shall apply the following standards to determine general recognition that a category of OTC drugs is safe and effective and not misbranded:

(i) Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(ii) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.111(a)(5)(ii) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(iii) The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness.

(iv) An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

(v) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use

(vi) A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs.

(5) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner a report containing its conclusions and recom-

mendations with respect to the conditions under which OTC drugs falling within the category covered by the panel are generally recognized as safe and effective and not misbranded. Included within this report shall be:

(i) A recommended monograph or monographs covering the category of OTC drugs and establishing conditions under which the drugs involved are generally recognized as safe and effective and not misbranded. This monograph may include any conditions relating to active ingredients, labeling indications, warnings and adequate directions for use, prescription or OTC status, and any other conditions necessary and appropriate for the safety and effectiveness of drugs covered by the monograph.

(ii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding.

(iii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that the available data are insufficient to classify such condition under either paragraph (a)(5) (i) or (ii) of this section and for which further testing is therefore required. The report may recommend the type of further testing required and the time period within which it might reasonably be concluded.

(6) *Proposed monograph.* After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing:

(i) A monograph or monographs establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded.

(ii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding.

(iii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that the available data are insufficient to classify such conditions under either paragraph (a)(6) (i) or (ii) of this section.

(iv) The full report(s) of the panel to the Commissioner.

The proposed order shall specify a reasonable period of time within which conditions falling within paragraph (a)(6)(iii) of this section may be continued in marketed products while the data necessary to support them are being obtained for evaluation by the Food and Drug Administration. The summary minutes of the panel meetings shall be made available to interested persons upon request. Any interested person may, within 60 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Hearing Clerk during regular working hours, Monday through Friday. Within 30 days after the final day for submission of comments, reply comments may be filed with the Hearing Clerk; these comments shall be utilized to reply to comments made by other interested persons and not to reiterate a position. The Commissioner may satisfy this requirement by publishing in the FEDERAL REGISTER a proposed order summarizing the full report of the advisory review panel, containing its conclusions and recommendations, to obtain full public comment before undertaking his own evaluation and decision on the matters involved.

(7) *Tentative final monograph.* After reviewing all comments and reply comments, the Commissioner shall publish in the FEDERAL REGISTER a tentative order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. Within 30 days, any interested party may file with the Hearing Clerk of the Food and Drug Administration written objections specifying with particularity the omissions or additions requested. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(8) *Oral hearing before the Commissioner.* After reviewing objections filed in response to the tentative final monograph, the Commissioner, if he finds reasonable grounds in support thereof, shall by notice in the FEDERAL REGISTER schedule an oral hearing. The notice scheduling an oral hearing shall specify the length of the hearing and how the time shall be divided among the parties requesting the hearing. The hearing shall be conducted by the Commissioner and may not be delegated.

(9) *Final monograph.* After reviewing the objections and considering the arguments made at any oral hearing, the Commissioner shall publish in the FEDERAL REGISTER a final order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. The monograph shall become effective as specified in the order.

(10) *Court appeal.* The monograph contained in the final order constitutes final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner may, at his discretion, stay the effective date for part or all of the monograph pending appeal and final court adjudication.

(11) *Amendment of monographs.* The Commissioner may propose on his own initiative to amend or repeal any monograph established pursuant to this section. Any interested person may petition the Commissioner for such proposal. A petition shall set forth the action requested and a detailed statement of the grounds in support of such action. After review of a petition, the Commissioner may deny the petition if he finds a lack of safety or effectiveness employing the standards in paragraph (a)(4) of this section (in which case the appeal provisions of paragraph (a)(10) of this section shall apply) or he may publish a proposed amendment or repeal in the FEDERAL REGISTER if he finds general recognition of safety and effectiveness employing the standards in paragraph (a)(4) of this section (in which case the provisions of paragraph (a) (6), (7), (8), and (9) of this section shall apply). A new-drug application may be submitted in lieu of or in addition to a petition under this paragraph.

(b) *Regulatory action.* Any product which fails to conform to an applicable monograph after its effective date is liable to regulatory action.

§ 330.11 NDA deviations from applicable monograph.

A new-drug application requesting approval of an OTC drug deviating in any respect from a monograph that has become final shall be in the form required by § 314.1(a)(2) of this chapter, but shall include a statement that the product meets all conditions of the applicable monograph except for the deviation for which approval is requested and may omit all information except that pertinent to the deviation.

Mr. FOUNTAIN. These regulations provide for the establishment of advisory panels to review OTC drugs, and for the promulgation of monographs for classes of drugs which apparently will serve as a basis for determining whether OTC drugs on the market are generally recognized as safe and effective and are not misbranded.

Is that description correct?

Mr. HUTT. Yes, sir. The only thing I would clarify is the use of the word "apparently." The regulations say that any product which fails to conform to an applicable monograph after its effective date is liable to regulatory action.

Mr. FOUNTAIN. I am also inserting into the record a notice which appeared in the September 7, 1973, Federal Register announcing an intended safety and efficacy review of OTC antiperspirants. The notice requested interested persons to submit to FDA by November 9, 1973, their safety and effectiveness data and other information for antiperspirant chemical entities, including zirconium compounds, for study by the review panel.

[The document referred to follows:]

[Federal Register, Vol. 38, No. 173—Friday, Sept. 7, 1973]

OVER-THE-COUNTER ANTIPERSPIRANT DRUG PRODUCTS AND OVER-THE-COUNTER TOPICAL ANTIBIOTIC DRUGS

SAFETY AND EFFICACY REVIEW; REQUEST FOR DATA AND INFORMATION

The FDA is undertaking a review of all over-the-counter (OTC) drug products for human use currently marketed in the United States, to determine that these OTC products are safe and effective for their labeled indications. This review will utilize expert panels working with FDA personnel.

A notice outlining procedures for this review was published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464).

To facilitate this review and a determination as to whether an OTC drug for human use is generally recognized as safe and effective and not misbranded under its recommended conditions of use, and to provide all interested persons an opportunity to present for the consideration of the reviewing experts the best data and information available to support the stated claims for all dosage forms of antiperspirant drug products and topical antibiotic drugs, the administration invites submission of data, published and unpublished, and other information pertinent to all active ingredients in such preparations.

FDA is aware that the following is not a complete list, but only representative of the kinds of active ingredients used in such products. FDA has conducted a literature search on each of them.

I. ANTIPERSPIRANTS

Aluminum Chlorhydroxide
Aluminum Chloride
Aluminum Formate
Aluminum Hydroxide
Aluminum Phenolsulfonate (Aluminum Sulfocarbolate)
Aluminum Sulfate
Aluminum Hydroxy Lactate
Sodium Aluminum Lactate
Aluminum Salts, General
Zinc Peroxide
Zinc Phenolsulfonate (Zinc Sulfocarbolate)
Zinc Salts, General
Zirconyl Hydroxychloride

II. TOPICAL ANTIBIOTICS

Bacitracin
Neomycin
Polymyxin
Gramicidin
Tyrothricin

FDA's literature search on antiperspirants covered the United States of America literature and other leading English language literature published since 1950 from the following sources:

Medlars (NLM and SUNY).
FDA Clinical Experience Abstracts.
Quarterly Cumulative Index Medicus.
Current List of Medical Literature.
Index Medicus.
JAMA Subject Index.
DeHaen Drugs in Use.
International Pharmaceutical Abstracts.
Excerpta Medica.
Abstracts of World Medicine.
Biological Abstracts.
Chemical Abstracts.

FDA's literature search on topical antibiotics covered the United States of America literature and other leading English language literature published since 1965 from the following sources:

Medlars (SUNY).
FDA Clinical Experience Abstracts.
DeHaen Drugs in Use.
RINGDOC.

The bibliographies of the literature searches are available to interested persons.

Interested persons are also invited to submit data on any other active ingredients used in antiperspirant or topical antibiotic drugs.

The FDA is aware that safety data on these ingredients may be available as a result of testing related to nondrug products, such as cosmetics. All interested parties are encouraged to submit at this time all available safety data for these ingredients, so that the conclusions reached will reflect the best information available.

This panel is not charged with reviewing the safety or effectiveness of the use of these ingredients in nondrug products such as cosmetics (e.g., deodorants for which no drug claims are made). However, the conclusions of the panel with respect to these ingredients for drug use may be utilized by the Food and Drug Administration in determining whether their use in cosmetics can continue to be justified. Thus, although the report and monograph prepared by this panel will cover only OTC drug use, the conclusions may well have a direct and substantial impact on all uses of these ingredients in consumer products.

To be considered, eight copies of the data and/or views must be submitted, preferably bound, indexed, and on standard size paper (approximately 8½ by 11 inches). All submissions must be in the format described below:

OTC DRUG REVIEW INFORMATION

I. Label(s) and all labeling (preferably mounted and filed with the other data—facsimile labeling is acceptable in lieu of actual container labeling).

II. A statement setting forth the quantities of active ingredients of the drug.

III. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

IV. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished product.

5. Pertinent medical and scientific literature.

V. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of the finished drug product.

5. Pertinent medical and scientific literature.

VI. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.

VII. If the submission is by a manufacturer, a statement signed by the person responsible for such submission, that to the best of his knowledge it includes unfavorable information, as well as any favorable information, known to him pertinent to an evaluation of the safety, effectiveness, and labeling of such a product. Thus, if any type of scientific data is submitted, a balanced submission of favorable and unfavorable data must be submitted. The same would be true of any other pertinent data or information submitted, such as consumer surveys or marketing results.

In order to avoid duplication, interested persons should not in their submissions include published literature listed in the FDA literature search. An abstract of all such literature will be provided to the panel. Upon request, the panel will be provided with the complete article. Interested persons may, of course, refer to such literature in their submissions by citation.

Submissions or requests for copies of the bibliographies of the FDA literature searches should be forwarded to:

Food and Drug Administration
Bureau of Drugs
OTC Drug Products Evaluation Staff (BD–109)
5600 Fishers Lane
Rockville, Maryland 20852

Data and information must be submitted on or before November 9, 1973.

Dated August 29, 1973.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc. 73–19007 Filed 9–6–73; 8:45 a.m.]

Mr. FOUNTAIN. FDA has provided the subcommittee with the minutes of all meetings of the panel, beginning with the first meeting on March 15, 1974, and going through the eighth meeting on January 30 and 31, 1975. The minutes of that last meeting held on or about March 25, 1975, have not been furnished.

Have the minutes of that meeting been prepared?

Mr. PINCO. The panel will take them up this week.

Mr. FOUNTAIN. And they will be made available soon thereafter?

Mr. PINCO. Yes.

Mr. FOUNTAIN. We have been using the terms "antiperspirants" and "antiperspirant deodorants." What do these terms mean?

Dr. SCHMIDT. An antiperspirant is commonly thought to be a product which inhibits the secretion of the glands and cuts down on the volume, if you like, of perspiration. The deodorant is commonly thought to protect against the odors which evolve from the interaction of bacteria and products from the skin as well as perspiration.

These can be separable terms, but they are commonly used synonymously in the case of underarm preparations which generally both inhibit perspiration, the volume of it, and inhibit the development of the typical odor.

Mr. FOUNTAIN. How long have zirconium compounds been used in antiperspirant deodorants and in aerosol spray antiperspirants?

Dr. SCHMIDT. Aerosol antiperspirants, themselves as a class are fairly new. I believe zirconium has been used in them for about 4 years.

Mr. FOUNTAIN. As defined by the Federal Food, Drug, and Cosmetic Act, are zirconium antiperspirant deodorants classified as drugs or cosmetics?

Mr. HUTT. They are classified as drugs. Deodorants have always been classified by the Food and Drug Administration and the Federal Trade Commission as cosmetics, but antiperspirants are classified as drugs.

Mr. FOUNTAIN. Are any of them covered by approved new drug applications?

Mr. HUTT. The aerosol products?

Mr. FOUNTAIN. Yes, those containing zirconium.

Mr. HUTT. No, sir.

Mr. FOUNTAIN. Are there any aerosol antiperspirants on the market which do not contain zirconium compounds?

Dr. SCHMIDT. Yes.

Mr. FOUNTAIN. Will you tell us what they are?

Dr. SCHMIDT. There is a wide variety.

Mr. FOUNTAIN. Just a few examples.

Dr. SCHMIDT. All of the aerosols, which are numerous, except Sure, Secret and a new Arrid which also is being test marketed and contains zirconium. They also contain other antiperspirants, principally the aluminum compounds.

Mr. FOUNTAIN. Has the OTC antiperspirant review panel given any indication that the nonzirconium aerosol antiperspirants are not generally recognized as safe?

Dr. SCHMIDT. I would like to make a general statement here. The panel's work, like that of any other group, has all different kinds of processes going on which groups in general have. Until the panel has completed either a segment of its activity or all of their activities by promulgating its report, it is not fair, proper, nor even possible to say what it has done or is doing. The panel is in the middle of its process right now and will be taking up antiperspirants in general in its next few meetings, so it is not possible for me to state, nor would I want to second-guess, the panel on what its opinions will be.

Mr. FOUNTAIN. The answer is no, they have not given any indication that nonzirconium antiperspirants are not generally recognized as safe?

Dr. SCHMIDT. That statement is true but misleading in that it implies more than would be the case. They have not done either.

Mr. FOUNTAIN. I am talking about up to this date.

Dr. SCHMIDT. To this date they have made no statement about antiperspirants.

Mr. FOUNTAIN. What about aluminum compounds?

Dr. SCHMIDT. Other than zirconium?

Mr. FOUNTAIN. What about aluminum compounds?

Dr. SCHMIDT. They are in the process of evaluating those.

Mr. FOUNTAIN. What advantages, if any, do zirconium-containing aerosol antiperspirants have over those which do not contain zirconium compounds, if you know?

Dr. SCHMIDT. There is a conventional wisdom, but again I am awaiting a report from the panel to me on the zirconium-containing products. Until I see that and evaluate it, I cannot answer the question.

Mr. HUTT. There is a legal problem here which, I think, I should state. It would be improper for the Commissioner to prejudge any of the issues of safety and effectiveness which may arise out of this panel. If he were to do so, he would be forced to disqualify himself from later considering any report that panel might issue. I would hope we would not get into areas today of trying to decide safety and effectiveness or labeling issues which are pending before the panel and which will ultimately come to the Commissioner.

Mr. FOUNTAIN. As I read the law, if a drug is not generally recognized as safe among experts qualified by scientific training and experience to evaluate the safety of drugs for the conditions for which it is to be used, it is a new drug. Is that interpretation of the law correct?

Mr. HUTT. Yes, sir, with certain exceptions under the grandfather clause which certainly do not apply to these products.

Mr. FOUNTAIN. We understand that.

As a new drug, it may not be marketed commercially in interstate commerce until a new drug application for it has been filed with, and approved by, FDA. Is that correct?

Mr. HUTT. That is correct. Of course, the purpose of the OTC drug review is to decide which are new drugs.

Mr. FOUNTAIN. What is the legal status of stocks of a new drug which have been shipped from one State to another without an approved new drug application? Are such stocks legal or illegal?

Mr. HUTT. Illegal.

Mr. FOUNTAIN. Would they be subject to seizure under the Federal Food, Drug, and Cosmetic Act?

Mr. HUTT. They would be subject to injunction, seizure, and to criminal action against the corporation and the individual who shipped them.

Mr. FOUNTAIN. You have taken such regulatory actions?

Mr. HUTT. Yes, sir, in the past, against other products, but not these.

Mr. FOUNTAIN. When FDA decides that a new drug must be removed from the market because an NDA for the drug has not been filed, must FDA prove that the drug is unsafe, in the event the removal action is challenged in court?

Mr. HUTT. No, sir. We must prove that it is not generally recognized as safe or not generally recognized as effective. We have the burden of proof of establishing that it is a new drug.

Mr. FOUNTAIN. Returning to the subject of antiperspirants, the subcommittee has examined the minutes of all of the meetings held by the antiperspirant review panel through January 1975. Those minutes, in my opinion, provide an adequate chronology of events in the panel's review of zirconium-containing antiperspirants. I believe we should take the time to develop the information contained in them as an authentic source of the facts in this matter.

The minutes disclose that aerosol antiperspirants containing zirconium compounds were first discussed by the panel during its third meeting on July 9 and 10, 1974. I am placing pages 1, 2, and 3 of the minutes of that meeting into the record. They cover the remarks to the panel by Prof. Joseph Page of Georgetown University Law School, Washington, D.C.

[The information referred to follows:]

The FDA OTC Antiperspirant Panel met for the third time on July 9–10, 1974 at the Parklawn Building. All members attended except Dr. Charles Evans.

Open Session—July 9, 1974—9:00–10:00 a.m.

Professor Joseph Page of Georgetown University appeared before the Panel and also provided them a written statement of his views. Professor Page reviewed the statement of the OTC Antimicrobial Panel which presents their concern about the regulation of antimicrobial soaps as drugs and cosmetics where the active ingredients are the same.

Professor Page was concerned that ingredients classified in Category II by the Panel or moved in the future from Category III to Category II might escape regulation by "hiding" under Cosmetic labeling.

He stressed his view that some ingredients placed in Category II by the Panel when labeled in antiperspirants as "drugs" would be regulated; however, if a product were relabeled only as a deodorant, there might not be sufficient evidence of toxicity to allow the FDA to make the judgment that cosmetics containing it are adulterated or misbranded.

Professor Page felt that the Antimicrobial I Panel's language had gone about as far as possible in their statement that as long as the ingredients of these products are effectively regulated, the Panel is not concerned whether they be classified as cosmetics or as drugs. They stated that, if a regulation can be promulgated imposing the kind of testing requirements recommended in their report upon all cosmetics containing antimicrobial ingredients at levels higher than necessary for preservative use, the Panel's concerns would be met. The Panel also recommended to the Food and Drug Administration that if this is not possible that they would urge Congress to furnish the necessary authority.

Professor Page felt that it is very likely that the Antiperspirant Panel will be faced with many of these same distinctions between cosmetic and drug definitions in reviewing labeling where the same ingredients are labeled as deodorants and antiperspirants.

In discussion with the Panel, the point was strongly made that the distinction between and definitions of a drug and cosmetic had been extensively discussed with the FDA legal counsel and that the Panel was proceeding on the basis of that discussion. The Panel had concluded from their discussion that their concern should be for the safety and effectiveness of the ingredients and that they need not be overly involved with definitions.

In discussing a second subject, Professor Page voiced his concern about the widespread advertising and sale of antiperspirants containing zirconium salts or zirconyl compounds. He reflected on the earlier marketing, in the 60's, of roll-on products containing zirconium salts which were shown to produce topical granulomas in the axilla. He told the Panel that he was not sure that these products had been adequately tested for safety of the aerosolized zirconium salts.

He stressed that for the product referred to, no NDA was submitted and that as far as he knew no submission on the product had been made to the OTC Panel. He reflected that one aerosol antiperspirant had been removed from the market and praised the responsible behavior of the manufacturer. He urged the Panel to review the information at hand on zirconium salts in liquid and aerosol formulations and try to determine if the review of these products should be undertaken immediately in the event that there is really a hazard to the public. A Panel member was designated to review the literature and communicate with experts to determine whether an immediate review by the Panel is required as was suggested by Professor Page's presentation. The industry liaison member of the Panel was asked to communicate the Panel's request for data to the companies involved.

Closed Session—July 9–10, 1974

The Chairman began with a review of activities from Panel members who are working on a series of subcommittees of the Panel; primarily, organizing data and screening material for review by the entire Panel. The sub committee planning the review of aerosol toxicity is collecting data and has requested all pertinent data on zirconyl-aluminum chlorhydroxide combinations in aerosol antiperspirants from manufacturers of these products and from the FDA. This group distributed copies of some references to the entire Panel. They are concentrating on the acquisition of material concerning particle size, dose-response data, determination of animal species for testing and the appropriate design of such tests.

Mr. FOUNTAIN. Two sentences appearing at page 3 of the minutes reflect Professor Page's views, as follows:

He reflected that one aerosol antiperspirant had been removed from the market and praised the responsible behavior of the manufacturer. He urged the panel to review the information at hand on zirconium salts in liquid and aerosol formulations and try to determine if the review of these products should be undertaken immediately in the event that there is really a hazard to the public.

Would you identify the aerosol antiperspirant that Professor Page said had been removed from the market and its manufacturer?

Dr. SCHMIDT. That was Gillette which had marketed a zirconium-containing product which had been termed "extra-strength". It was a trade name already marketed, Right Guard. This was an extra-strength Right Guard.

Mr. FOUNTAIN. In this connection I am placing into the record FDA's October 10, 1973, Talk Paper describing Gillette's recall of Right Guard. I think I saw some on my table in the bathroom this morning in my own apartment.

Mr. HUTT. Mr. Chairman, it is not the Right Guard that you would have had on your shelf this morning, to my knowledge, unless it somehow escaped detection. That brand name has been used for aluminum products and also for the zirconium product. It is the aluminum product you had on your shelf. The zirconium product has been withdrawn from the market by the company.

Mr. FOUNTAIN. I have no idea.

Mr. HUTT. The active ingredients are on the label.

Mr. FOUNTAIN. As with most consumers, I have not paid much attention to the label. Perhaps I depend on you to protect me.

[The document referred to follows:]

FDA TALK PAPER [1]

Rockville, Md., October 10,1973.

GILLETTE COMPANY RECALL

The Gillette recall of October 1, 1973 has generated considerable discussion within the industry about products with similar formulation. The following is provided to aid in responding to queries.

The Gillette Company has provided FDA with the preliminary data used by the Company in deciding to recall Right Guard Extra-Strength Anti-Perspirant, and Soft and Dri Extra-Strength Anti-Perspirant. This data showed inflammations in the lungs of monkeys subjected to repeated high level exposure. Both products are new, but only the Right Guard Extra-Strength product reached retail outlets. Other Right Guard and Soft and Dri Aerosol Anti-Perspirant preparations are not involved in this recall.

Gillette's study also included a competitive product, Procter & Gamble's Sure Anti-Perspirant. While some lung inflamation was observed in monkeys tested with Sure, the results were not the same as with the two Gillette products. The formulations of the Procter & Gamble product and the Gillette products are somewhat different. Procter & Gamble has conducted similar studies on Sure. These studies will be provided to FDA shortly. The data now available to FDA does not indicate the need for regulatory action. FDA has, however, assigned a special team to expedite the evaluation of all data to determine if a question of safety exists which would require action on similar products.

In addition, FDA has underway a comprehensive program to identify and evaluate the safety of all OTC and Rx aerosol drug products on the market.

Mr. FOUNTAIN. Of significance, I think, is this statement appearing in the Talk Paper:

The Gillette Co. has provided FDA with the preliminary data * * *. This data showed inflammations in the lungs of monkeys subjected to repeated high level exposure.

According to the minutes of the July 9 and 10 meeting, Dr. Page also told the panel:

* * * Professor Page voiced his concern about the widespread advertising and sale of antiperspirants containing zirconium salts or zirconyl compounds. He reflected on the earlier marketing, in the sixties, of roll-on products containing

[1] FDA Talk Papers are issued by the FDA Press Office to provide guidance to FDA personnel in responding to requests for information on subjects of current interest. They are subject to change as more information or data becomes available.

zirconium salts which were shown to produce topical granulomas in the axilla. He told the Panel that he was not sure that these products had been adequately tested for safety of the aerosolized zirconium salts. He stressed that for the product referred to, no NDA was submitted and that as far as he knew no submission on the product had been made to the OTC Panel.

Is it true, as the minutes state, no NDA's have been submitted for these aerosol zirconium antiperspirant sprays now on the market?

Dr. SCHMIDT. Yes, sir.

Mr. FOUNTAIN. Is it also true, as the minutes state, that as of July 9, 1974, the firms marketing those sprays had made no submissions on the products for panel consideration?

Mr. HUTT. I cannot state. Perhaps Mr. Pinco can do this.

Mr. PINCO. There are two points. I understand there was a submission, an abbreviated new drug application, back in 1972 with regard to the Sure product. That was stayed pending OTC review.

Mr. FOUNTAIN. Was that an aerosol?

Mr. PINCO. Yes. I believe it was Sure antiperspirant aerosol. I cannot give the date we received it but we can check on that and give it to you.

Mr. FOUNTAIN. Will you check that and submit it for the record.

Mr. PINCO. Yes, sir.

[NOTE.—See pp. 53–55 for further discussion and document on this.]

Mr. FOUNTAIN. The minutes should cover this. Have you checked those out?

Mr. PINCO. That would not be in the minutes. My understanding is that the Sure product was covered by a submission when the call for data went out. That submission was not subsequently made as a special submission at a later date. However, we will check that. We are going on memory here.

Mr. GOLDHAMMER. In my investigation I was informed that the manufacturer of Sure—Procter & Gamble—had not made a submission; and that a later opportunity was given. Their submission was made at a later date, but not at the time of the call for data, which, I believe, might have been in May.

Mr. PINCO. Mr. Goldhammer, we will have to check that. Our recollection was they made some earlier submission. We may be wrong. It is entirely possible it could have come in later.

[NOTE.—FDA subsequently advised the subcommittee that the Sure and Secret submission to the OTC panel was made in August 1974.]

Mr. FOUNTAIN. The minutes of the review panel meeting of July 9 and 10, 1974, also disclose that the panel acted on Dr. Page's request. It designated a panel member to review the literature and communicate with experts to determine whether an immediate panel review of the subject was required. The minutes of the review panel's fourth meeting on August 8 and 9, 1974, disclose that the designated panel member reported to the panel on his review of the literature on zirconium in antiperspirants. I am placing the cover sheet and pages 9 and 10 of the minutes into the hearing record. I think they summarize the panel's observations after discussing the available data.

[The information follows:]

SUMMARY MINUTES—FDA—OTC ANTIPERSPIRANT PANEL

[Fourth Meeting, Parklawn Building, Rockville, Md., August 8–9, 1974]

Chairman.—E. William Rosenberg, M.D.
Executive Secretary.—Mary K. Bruch.
Panel Members:
J. Wesley Clayton, Ph. D.
Charles Evans, M.D., Ph. D.
Zenona Mally, M.D.
Jane Rosenzweig, M.D.
Robert Scheuplein, M.D.
Eli Shefter, Ph. D.
Industrial Liaison.—CTFA—Robert Giovacchini, Ph. D.
Consumer Liaison.—Consumer Federation of America—Marsha Gardner.
FDA Representatives.—Bureau of Foods:
Leonard J. Trilling, M.D.
Mr. Heinz Eiermann.
OTC Staff:
Panel Administrator—Lee Geismar.
Drug Information Analyst—Gary Troseclair.

1. We know from the past medical literature and experience that sodium zirconium lactate can cause skin granulomas and granuloma formation in the lungs.

2. A variety of granuloma formations have been seen in animals and some in humans from zirconium oxide which is present in poison ivy remedies.

3. A presently marketed antiperspirant contains zirconium oxychloride (zirconium chlorhydrate) as part of a complex with aluminum chlorhydrate. The manufacturer has conducted short-term studies in animals and claims no toxic effects were found. Topical granulomas have been produced in individuals who previously reacted to sodium zirconium lactate with one element of the complex, zirconium oxychloride.

4. Complete complaint files have been requested from the manufacturer of the marketed product containing zirconium oxychloride. The product complaints received by the FDA are also being examined.

5. One manufacturer has voluntarily recalled two products containing zirconium oxychloride after a granulomatous response was noted in monkeys who were exposed to the product in inhalation tests. This test was repeated in monkeys and the same response was elicited again.

6. The Panel has received data from inhalation studies in monkeys for different formulations which do not produce granulomatous lesions under the test conditions.

The Panel felt that many questions raised by their discussion can be resolved in open discussion with recognized experts. They also decided as a result of their discussion and review of the data they presently have to alter the course of their review and consider zirconyl-containing antiperspirants including aerosols as soon as scheduling will permit.

Mr. Gary Yingling, a representative from the FDA Legal Counsel's Office, was asked by the Panel to clarify some regulatory points raised by their discussions.

Mr. Yingling revealed that an ingredient which has not been marketed in the United States cannot be marketed through OTC monograph amendment procedures but must be regulated through the IND/NDA procedures. This would also apply to new ingredients never previously marketed.

Mr. Gary Yingling reviewed the three categories and the procedures to be followed by FDA and the manufacturers subsequent to final categorization by the Panel. The consequences of placement in Category II and timing of NDA application, if it is required, were reviewed. Mr. Yingling told the Panel that a product containing a Category II ingredient would be removed from the market unless there were an approved NDA at the specified time period when the provisions of the monograph became final. * * *

Mr. FOUNTAIN. If you gentlemen feel anything else should go in, don't hesitate to let us know.

On page 10 the minutes state:

> The panel felt that many questions raised by their discussion can be resolved in open discussion with recognized experts. They also decided as a result of their discussion and review of the data they presently have to alter the course of their review and consider zirconyl-containing antiperspirants including aerosols as soon as scheduling will permit.

The word "zirconyl" in this quote is different from zirconium which I have been using. I am informed, however, the two words are essentially interchangeable in this context. Is that right?

Dr. SCHMIDT. Well, yes and no. They both indicate the base zirconium. There is some discussion about different chemical complexes which zirconium can enter into and whether or not there are different safety aspects to zirconium in one particular complex as opposed to another or just elemental substance.

Mr. FOUNTAIN. I am also placing into the record pages 13 and 14 of the minutes which contain a bibliography of papers mostly on granulomas associated with the application or inhalation of zirconyl compounds.

[The material referred to follows:]

REFERENCES

(1) Baler, G. R., "Granulomas from Topical Zirconium in Poison Ivy Dermatitis," *Archives of Dermatology*, 91: 145–148, 1965.

(2) Epstein, W. L., and J. R. Allen, "Granulomatous Hypersensitivity After Use of Zirconium-Containing Poison Oak Lotions," *Journal of the American Medical Association*, 190: 162–164, 1964.

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(5) Kozikowski, E. S., "Granuloma of the Axillae," *American Medical Association Archives of Dermatology*, 75: 892, 1957.

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(11) Rubin, L. S., and A. H. Slepyan, L. F. Weber and I. Neuhauser, "Granulomas of the Axillae Caused by Deodorants," *Journal of the American Medical Association*, 162: 953–956, 1956.

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Mr. FOUNTAIN. The panel's fifth meeting was held on September 19 through 21, 1974. Zirconyl antiperspirants were not discussed at this

meeting apparently. However, the last two sentences of the minutes of that meeting indicate that the panel agreed to discuss granuloma production with zirconium compounds in both topical and aerosol antiperspirants at its sixth meeting.

The minutes of the panel's sixth meeting on October 31 to November 2, 1974, are lengthy, consisting of some 47 pages. They describe presentations made by a number of experts in granuloma formation, and the action of zirconyl antiperspirants. Representatives of Procter & Gamble and their consultants also made presentations to the panel. I am placing into the record the cover sheet and pages 43 through 47 of those minutes which cover the panel's discussions.

[The information follows:]

SUMMARY MINUTES OF THE OTC PANEL ON ANTIPERSPIRANT DRUG PRODUCTS

[Sixth Meeting, October 31-November 2, 1974, Parklawn Building, Rockville, Md.

Panel Members:
E. William Rosenberg, M.D., Chairman.
Zenona Mally, M.D.
Charles Evans, M.D., Ph. D.
Jane Rosenzweig, M.D.
Eli Shefter, Ph. D.
Robert Scheplein, Ph. D.
J. Wesley Clayton, Ph. D. (Absent November 2).

Liaison Members:
Consumer.—Ms. Marsha Gardner.
Industry.—Robert Giovacchini, Ph. D.

FDA Staff Members:
Mary K. Bruch, Executive Secretary—Division Anti-Infective Drug Products.
Lee Geismar, Panel Administrator—OTC Staff.
Joe Hussion, R.Ph., Drug Information Analyst—OTC Staff.
Gary L. Yingling, Esq., General Counsel's Office.
J. Richard Crout, M.D., Director, Bureau of Drugs.

* * * * * * *

CLOSED SESSIONS

A short closed session was held on Friday afternoon. The views of Panel members were surveyed. Some felt strongly that zirconium aerosols should be in Category II and gave their reasoning for their view of the highly disproportionate risk/benefit determination. Other members felt the situation was very serious but expressed the view that perhaps better testing would answer their concerns, provided such tests could be successfully done. Members asked for a clarification of the meaning of safety, effectiveness and risk/benefit ratio. Mr. Yingling of Counsel's Office provided this and responded to requests to explain the consequence of Category II and III placement. Most members asked for the evening to sort their thoughts before a final determination.

A second closed session was held at 8:30 a.m. on Saturday, November 2, 1974 at the United Inn in Bethesda, Maryland. Members again discussed their views, constructing risk and benefit lists. The vote on a motion to categorize zirconium containing aerosol antiperspirants in category II was 6 to 0 (one Panel member was absent), but later voted to make the vote unanimous.

The potential toxicity of these ingredients in antiperspirants was of such concern that the Panel voted unanimously to request that the normal course of the designated review process be interrupted. They agreed to prepare a statement to present to the Commissioner in the immediate future detailing the reasoning supporting their vote as to why it is inappropriate for the products to remain on the market and requesting that this be published in the Federal Register. They did not intend to suggest or recommend a recall.

A vote was also taken on a motion to categorize zirconium chlorhydrate in cream, liquid or pad (where application is directly on the skin and not aerosolized) into Category I on the basis of safety. Effectiveness is yet to be reviewed.

The following statement includes the Panel's supporting reasons for their action. This is in draft form and will be revised.

The benefits of aerosol application appear negligible or nil; in fact, the effectiveness as deduced from laboratory test appears comparable or less when the zirconium complex is applied as an aerosol than it is when applied as a liquid or cream. The only benefit is perhaps the illusory increment in the ease of application. Balanced against this, are what we consider the following risks:

1. Zirconium salts are well known to produce granulomas in the skin of some sensitized subjects (Publication by W. Epstein). While these subjects were all made allergic by the sodium zirconium salt, it has been shown that zirconium chlorhydrate (Ref.—adopted name, CTFA Dictionary) is capable of eliciting a granulomatous response in already sensitized human subjects (Procter and Gamble submission to OTC Review).

2. Manufacturers of marketed aerosol products containing zirconium chlorhydrate as a part of a complex or mixture were unable to prove that simple zirconium chlorhydrate (same as zirconium hydroxychloride) is not liberated upon deposition in contact with lung tissue (statement to OTC Panel by Procter and Gamble, November 1, 1974).

3. Testing of presently marketed aerosol antiperspirants containing zirconium chlorhydrate was inadequate in both quantity and quality to demonstrate the absence of granulomatogenic properties according to recognized experts (statement of Dr. Boros to OTC Panel, November 1, 1974).

4. At least one major manufacturer who tested an aerosol of this general class (a differently compounded complex of zirconium and aluminum chlorhydrate) discovered at least 20 incidences of pathologic changes in monkey lungs. These alterations were described by authorities as consistent with early changes of a granulomatous nature.

5. Granulomatous diseases of the lung (sarcoid-like or sarcoid diseases) are notoriously difficult to diagnose and may cause few or no symptions until quite advanced. According to one manufactuer of zirconium-containing antiperspirants, some one hundred million Americans have used the product at least once. If this product should turn out to have even a modest granulomatogenic potential, the problems it would cause are of enormous magnitude, both in numbers and in possible seriousness in those affected.

6. Experts in the field of aerosol toxicology have pointed out that some particulate matter can remain suspended in the air for several hours after use. Because aerosol antiperspirants are used in small bathrooms, which are subsequently used by other members of the family (including children, pregnant women and persons with impaired pulmonary status), the risk would be magnified. Moreover, since zirconium induced granulomas appear in some instances to be produced by mechanisms of delayed hypersensitivity, even minute exposure to this secondary source might be enough to evoke disease.

7. Certain granulomatous diseases of the lung (berylliosis and silicosis) are worse when associated with other pulmonary irritant disorders, such as infection or cigarette smoking. The precise etiology of such multi-factorially induced diseases has been in the past, difficult to elucidate by epidemiologic means. If the Panel is to wait for clear-cut epidemiologic evidence of the causative role of zirconium salts in producing lung disease, substantial numbers of persons may be exposed to risk before the issue is settled.

8. In addition, the nearly ubiquitous distribution of these products will make epidemiologic studies even more difficult.

9. Epithelioid cells and giant cells are a characteristic of previously reported zirconium granulomas. Recent studies of the epithelioid cell and giant cell show substantial DNA turnover and abnormal mitotic figures whose biological potential in unknown.

Suggestions were made during the scientific presentation in the open session that the toxicity of other aerosol antiperspirants be reviewed soon. This subject will be initiated at the Panel's next meeting on December 16 and 17.

Prepared by: Mary K. Bruch, Executive Secretary.

Mr. FOUNTAIN. Of particular significance is the following excerpt from the minutes at page 43:

A short closed session was held on Friday afternoon. The views of panel members were surveyed. Some felt strongly that zirconium aerosols should be in category II * * *.

I have been informed that in the OTC drug reviews category II is reserved for those drugs or drug ingredients not generally recognized as safe or effective among qualified experts. Is that definition correct?

Mr. PINCO. That is correct, Mr. Fountain.

Mr. FOUNTAIN. And category II drugs, therefore, would be new drugs requiring a new drug application. Is that correct?

Mr. PINCO. Yes, sir.

Mr. FOUNTAIN. What other categories are there for antiperspirant ingredients classified by the review panel, Doctor?

Dr. SCHMIDT. Category I, of course, are those ingredients which can be termed as safe and effective under the conditions specified. Category III is one in which there are no data sufficient to make a judgment and for which additional data are required.

Mr. FOUNTAIN. Page 44 of the minutes of the panel's sixth meeting indicates:

A second closed session was held at 8:30 a.m. on Saturday, November 2, 1974, at the United Inn in Bethesda, Md. Members again discussed their views, constructing risk and benefit lists. The vote on a motion to categorize zirconium containing aerosol antiperspirants in category II was 6 to 0 (one panel member was absent), but later voted to make the vote unanimous.

The minutes also state at page 44, and again I quote:

The potential toxicity of these ingredients in antiperspirants was of such concern that the Panel voted unanimously to request that the normal course of the designated review process be interrupted. They agreed to prepare a statement to present to the Commissioner in the immediate future detailing the reasoning supporting their vote as to why it is inappropriate for the products to remain on the market and requesting that this be published in the Federal Register. They did not intend to suggest or recommend a recall.

On November 27 the panel issued a 21-page statement to set forth its position on aerosol antiperspirants containing zirconium, and I am placing a copy of that statement in the record.

[The statement referred to follows:]

STATEMENT OF THE PANEL ON AEROSOL ANTIPERSPIRANTS CONTAINING ZIRCONIUM, NOVEMBER 27, 1974

I. INTRODUCTION

Consumer groups (Ref. 1) requested the Panel to pay particular attention to the safety questions raised by the use of certain zirconium-containing compounds in aerosol antiperspirants. The background of their request was the documented record that certain other zirconium compounds had previously caused granulomatous disease of the skin when used as antiperspirants and poison ivy remedies (Shelly and Hurley, Ref. 2).

Because some aerosolized particles are known to reach the lungs, and because the lung is one of the organs of the body especially prone to granulomatous disease, the Panel decided to assess the risk to the lungs of presently marketed zirconium-containing aerosol antiperspirants.

This report is a statement of our present position after discussing this problem at both open and closed meetings. It includes an analysis of the benefit to risk considerations as we believe them to apply here.

II. SAFETY OF ZIRCONIUM PRODUCTS

(*a*) *Nature of the Granuloma*

Since its tendency to induce granulomas is the basis for the Panel's concern about zirconium, we will summarize very briefly what is meant by the term,

granuloma. The granuloma (Ref. 3) is considered to be a distinctive form of inflammatory reaction which results when cells of the mononuclear phagocyte system encounter some substance they are unable to eliminate effectively.

The cells of the mononuclear phagocyte system are scavenger cells, widely dispersed throughout the body. It is now recognized that they are all derived from a common precursor (source) cell in the bone marrow. Depending on where they are located in the body, they take on different appearances and are called by different names. These locations and names include circulating blood (monocytes), connective tissue (histiocytes), liver (Kupffer cells), lungs (alveolar macrophages), lymph nodes (free and fixed macrophages), bone marrow (macrophages), serous cavity (pleural and peritoneal macrophages). The osteoclast (bone tissue) and the microglial cells of the nervous system are probably also cells of this type.

As long as these cells are effectively able to remove foreign substances from their respective tissue no unusual cell accumulation occurs. It is thought that in at least three instances this effective elimination of foreign substances is impaired and cells derived from mononuclear phagocytes accumulate. The term granuloma is used for the lesion produced by those accumulated cells.

One such instance occurs when the foreign substance has low biological activity for which there is no effective mechanism of elimination. Here the mononuclear phagocytic cells become stuffed with material that resists the cell's degradative enzyme system. These cells are immobile, resistant, long-lived macrophages which do not divide. These cells store the offending substance, often over a prolonged period. The granuloma thus formed is metabolically relatively inactive and has been termed, a "low turnover" granuloma.

A different form of granuloma occurs in two other instances. In one of these, the foreign substance is toxic to the scavenger cell and damages it, releasing further toxic material into the tissue. In the other, the foreign substance acts as an allergen and brings cells of the body's immune system into play. In both of these cases, when the foreign substance is toxic or when it acts as an allergen, the resulting granuloma is characterized by a metabolically very active derivative of the mononuclear phagocyte called the epithelioid cell and also a form called the giant cell. Such granulomas are now termed, "high turnover" granulomas.

Unlike the low turnover granulomas in whose cells the offending agent is easily found, the cells of the high turnover granulomas usually do not reveal the presence of the causative agent. The epithelioid cell granuloma has thus been more difficult to study and understand. More recently, however, it has been found that present techniques of immunology have helped to clarify the nature of high turnover granulomas caused by immune mechanisms (Ref. 3).

Of considerable interest is the recent observation that the mononuclear phagocytic cells of the granuloma produce a substance which acts as a stimulant to nearby connective tissue fibroblast cells. These fibroblasts are stimulated to produce more collagen, the basic fiber of connective tissue.

This effect of granuloma cells on fibroblasts would seem to explain the tendency of chronic granulomatous disease of the lung to result in a condition called pulmonary fibrosis. In this condition the required mobility of the breathing process is interfered with by excessive amounts of connective tissue in the lung.

In current medical practice, a substantial amount of recognized granulomatous disease is of unknown cause. The term sarcoidosis is applied to one group of granulomatous changes whose cause is unknown but in which the clinical course often conforms to a recognizable pattern. Known causes of granulomatous disease are the bacterial products of the tuberculosis and leprosy bacilli, and some forms or compounds of metallic chemicals such as silicon, beryllium, and zirconium.

(b) Zirconium Compounds Are Cause of Granuloma

(i) Clinical experience

Shelly and Hurley (Ref. 2) provide a concise review of the experience of American dermatologists with the granulomas that were first noted soon after sodium zirconium lactate was introduced as an antiperspirant ingredient in the 1950s. At that time the zirconium compound was formulated in a stick that was rubbed on the underarm skin. A characteristic underarm eruption of small, indolent flesh-colored papules appeared, often occurring in linear streaks. The streaks suggested that the lesions followed introduction of the compound into the deeper parts of the skin through breaks in the skin caused by shaving nicks. The individual lesions resembled those seen in different distributions over the body in the disease called sarcoidosis. Biopsies of the lesions also revealed a resemblance to the lesions of sarcoidosis, the so called epithelioid cell granuloma (Refs. 4 through 10).

Several years later a different zirconium salt, zirconium oxide, was introduced for use on the skin, this time as the treatment for poison ivy dermatitis. Again, the areas of skin treated with the zirconium oxide cream broke out with small papules which when biopsied revealed epithelioid cell granulomas (Refs. 11 through 15).

(*ii*) *Mechanisms of zirconium-induced granulomas*

It was shortly established (Ref. 10) that the zirconium-induced granuloma of skin was the result of an allergic or hypersensitivity mechanism. These observations were later extended by Epstein (Ref. 16). The presence of an allergic mechanism which caused zirconium-induced granulomas would explain the epithelioid cell nature of the lesion, the fact that only some of those exposed to the product developed lesions, the minute quantities required to elicit a response, and the inability of investigators to find measurable quantities of zirconium in the lesion.

(*iii*) *Specificity of zirconium hypersensitivity*

An important question is the one of how general is the tendency of zirconium-containing compounds to produce granulomas. Clinical experience had shown that two such compounds, sodium zirconium lactate and zirconium oxide, would produce granulomas in the skin of sensitized individuals.

(An organized investigation, in which many different zirconium compounds of different chemical types could be tested has not been accomplished. This is because it has heretofore not been possible to induce a zirconium granuloma in a laboratory animal and testing in man has until lately been limited to techniques in which the investigator injects the test compound into the patient's skin and waits for the granuloma to develop. Such tests are obviously not suitable for large scale screening studies. Recent advances in the immunologic studies of granuloma formation suggest at least two possible avenues of study. These would include (1) attempts to utilize techniques used to study schistosome hypersensitivity in laboratory animals, and (2) non-invasive tests in which white cells from patients with known hypersensitivity to zirconium could be tested *in vitro* to different zirconium compounds (Refs. 3 and 17 through 22). We will refer to these possible methods of study later in this statement.)

Neither sodium zirconium lactate nor zirconium oxide are constituents of the zirconium-containing spray antiperspirants under review. The OTC products contain zirconium in the form of zirconium chlorhydrate which is then complexed with either aluminum chlorhydrate alone or with aluminum chlorhydrate plus glycine. Obviously it is the potential of these latter complexes to produce granuloma that most concerns the Panel.

Epstein (Ref. 3) performed a limited number of skin tests on subjects known to form skin granulomas when injected with sodium zirconium lactate. In one such patient he found that a skin test with a saline solution of zirconium chlorhydrate and also with a complex of zirconium chlorhydrate and glycine resulted in a skin granuloma comparable to those elicited by sodium zirconium lactate. In the same skin test report, however, Epstein stated that a specific complex of zirconium chlorhydrate, aluminum chlorhydrate, and glycine did not elicit a granulomatous response.

Epstein later reported (Ref. 3) that he was able to produce the zirconium-induced granulomas in two of three zirconium-sensitized subjects when tested with each of the following products: zirconium chlorhydrate, a complex of zirconium chlorhydrate and glycine, and a complex of zirconium chlorhydrate and aluminum acetate. Again the specific complex of zirconium chlorhydrate, aluminum chlorhydrate and glycine did not produce positive skin tests.

The evidence thus shows clearly that at least three zirconium compounds will induce epithelioid cell high turnover granulomas in man. These are sodium zirconium lactate, zirconium oxide, and zirconium chlorhydrate. Zirconium chlorhydrate, it must be noted, is the specific zirconium-containing moiety included in each of the antiperspirant complexes under review.

Claims of safety based on Epstein's negative findings with skin tests of a specific complex of zirconium chlorhydrate, aluminum chlorhydrate and glycine are not considered adequate by the Panel. In order for Epstein's test to demonstrate safety of the complex it would have to be established that the complex remains permanently intact and will not break down in the body into its constituent parts, one of which, zirconium chlorhydrate, is a known allergen. No evidence was provided to the Panel of the metabolic fate of the various zirconium-containing antiperspirants after exposure to the degradative mechanisms of the body.

No substantial evidence was presented that zirconium-containing complexes could not break down in the body to release zirconium chlorhydrate.

(*c*) *Zirconium in the Lung*

The Panel, even though it has evidence of zirconium-induced skin granulomas, does not have indisputable evidence of granulomas induced by zirconium in the lung. The potential problems of such lung disease, however, appear extremely serious to the Panel.

(*i*) *Access to the human lungs*

Data presented to the Panel (Ref. 3) show that in four different tests, 48, 59, 67 and 63 percent respectively, of the zirconium-containing particles released from an antiperspirant aerosol product were less than 5.5 microns in size. Inhaled particles of that size can gain "direct access to alveoli" according to Bernstein, Hatch and Gross, and Natusch and Wallace (Refs. 23 through 26). Bernstein also states that such particles cannot be extruded from alveoli and can cause foreign body reactions.

(*ii*) *Fate of inhaled particles*

We come now to the critical question of what happens to these zirconium complexes which have access to the alveolar macrophages. (It will be recalled that the alveolar macrophage is a term used for the mononuclear phagocytic cell that is found in the lung. Such mononuclear macrophages are entirely capable of undergoing transformation into the types of cells characteristic of a granuloma.)

(a) On the one hand there is the possibility that the complex of either zirconium chlorhydrate and aluminum chlorhydrate or the specific complex of zirconium chlorhydrate, aluminum chlorhydrate and glycine will, after deposition in the lung, undergo a process of degradation as a result of metabolic activity. Should this occur, it is likely that one of the breakdown products of that process will be zirconium chlorhydrate. As noted earlier, zirconium chlorhydrate is capable of eliciting a hypersensitivity granulomatous response in sensitized subjects. Thus, should it happen that the various complexes which contain zirconium chlorhydrate are broken down in the lung, it can be anticipated that some number of those exposed persons will exhibit an allergic type of granulomatous response to that zirconium chlorhydrate.

Despite repeated questions from the Panel at its open meeting on November 1, 1974, representatives of industry were unable to state what the metabolic fate of the various zirconium chlorhydrate-containing complexes in the lung would be. They had no information to show the fate of inhaled particles left in contact with lung surface.

(b) The second possibility, which was implied by manufacturers of one such complex was that their complex (zirconium chlorhydrate, aluminum chlorhydrate, glycine) was uniquely stable and was unlikely to break down in the lung. If this were in fact to be the case, we are still left with the question of how the body is to dispose of this unusual heavy metal complex that is now being brought to its lung surface. Comparable situations exist in industry where certain dusts, long thought to be inert, are now known to produce disease. These include the black lung of coal dust which typically occurs after 20 to 30 years of exposure to coal dust, silicosis which may occur only after a lapse of 20 years, and pulmonary effects of exposure to metallic iron ore, and tin (Ref. 27). For many years, it was thought that exposure to such inert dusts was harmless. It is now recognized they are not harmless and that pulmonary fibrosis may sometimes result from continued exposure to these dusts. Admittedly there is a vast individual variation and susceptibility to disease development as a result of exposure to such dusts. The way in which a person breathes, the effectiveness of the clearing action of his mucosal cilia, and the effectiveness of his alveolar macrophage function may all play a part. Also involved may be the presence or absence of cigarette smoking or other particulate contaminants in the air. In any case, the continued exposure of alveolar macrophages to even an inert heavy metal complex cannot be regarded as harmless, especially since the zirconium-containing complexes in question have been available in inhalant form only for the past four years and it is perhaps too early for the long term effects to have been documented by case reports.

(*iii*) *Zirconium in the lungs of animals*

Mogilezskaja (Ref. 28) reported on the effect of zirconium-containing aerosols in rats. She found that soluble salts of zirconium produced tissue damage in the lungs characteristic of a low-grade chronic irritation. The insoluble products did not produce obvious inflammation but did seem to provoke an increase of the fibrogenic reaction in the lung.

In 1960 Prior et al. found that when 6 albino rabbits were subjected to a 44 percent sodium zirconium lactate mist daily (at 20 minute intervals) for six weeks, all developed either bronchiolar abscesses with lobular type pneumonia or lung (peribronchial) granulomas (Ref. 29). Some animals developed granulomas in the liver, tongue and ear cartilage. All six control animals subjected to a similar pathological examination at the end of six weeks were free from clinical disease and granulomas.

There is further experience based on inhalation tests in monkeys of an antiperspirant complex composed of aluminum chlorhydrate and zirconium chlorhydrate. The results of those tests showed that all animals exposed developed either slight or mild degrees of exudative bronchiolitis. These results raised serious issues because the test described was a routine 90-day type of toxicologic test, which was not specifically designed to look for a tendency to produce granulomas. Such a short term test (lasting 90 days) would not be expected to reveal the kinds of long-term changes the Panel is concerned about.

(d) Statements from Industry Supporting the Safety of Zirconium

The Panel invited representatives of industry to present data supporting the safety of zirconium containing antiperspirants. The summary of their statements, and our analysis of them are as follows:

(i) The complex of zirconium chlorhydrate, aluminum chlorhydrate, and glycine has been used on the skin for 16 years (since 1958) with approximately 468 million units having been sold in various forms. No documented reports of granulomatous skin disease (such as quickly followed the marketing of sodium zirconium lactate sticks) have been made.

The Panel agrees that the marketing experience of the creams and liquids are reassuring about their safety and feels the creams and liquids are generally regarded as safe. The fact that the cream is safe, however, does not necessarily mean that an inhaled spray would also be safe, for the following reasons: (a) only small amounts of zirconium enter the skin, mostly through nicks and cuts, while a significant portion of inhaled spray particles can reach the lungs. (b) The ability of the skin and lung to rid themselves of foreign particles differs. (c) Metabolic degradation of foreign particles may differ in the two sites. (d) Diffuse fibrosis of the skin as a reaction to foreign substances is not a recognized clinical entity while pulmonary fibrosis due to a wide variety of chronically inhaled particles is a well known and very serious disorder.

(ii) The complex of zirconium chlorhydrate, aluminum chlorhydrate and glycine has been sold in aerosol spray form for 4 years and have been used by millions of persons.

This mass distribution of a product, apparently lacking adequate safety testing, did not reassure the Panel even though there were not a large number of reported cases of clinical disease. Despite the fact that the particle size distribution of the spray product makes it almost certain that some of the zirconium-containing complex reaches the lung, the Panel was given no information about how much reaches the lung, how it is either stored, degraded, or eliminated, or its final fate in the body. Furthermore, a period of 4 years would not be long enough to reveal a tendency to promote fibrosis; experience with other inhalation-induced diseases shows that it is not rare for a 20 year period to elapse before obvious symptoms begin to appear. The Panel was not satisfied by examination of one product's complaint record. The Panel was told that during a 5-month period in 1973, some 247 consumer complaints were received by one manufacturer including over 30 complaints of respiratory distress. The manufacturer was unable to tell us what sort of medical follow-up was made on any of these cases and it appeared, in fact, that none had been made at all, except by FDA inspectors. Such follow-up could have included, as a minimum, the taking of chest X-rays on these patients; zirconium in the lung is radio-opaque and in some instances will produce shadows.

(iii) The complex of zirconium chlorhydrate, aluminum chlorhydrate and glycine is chemically stable at body pH and unlikely to break apart.

Even if it remained intact, that complex might produce a low turnover granuloma with late onset pulmonary fibrosis in some subjects. The pulmonary macrophage, moreover, is known to produce many degradative enzymes (Ref. 30). Until the antiperspirant complex is exposed to comparable enzymes, the Panel cannot know that it will remain intact in the lung.

(iv) Even in patients known to form allergic granulomas from sodium zirconium lactate, skin tests with zirconium chlorhydrate, aluminum chlorhydrate and glycine complex were consistently negative.

In those same subjects, however, skin tests with plain zirconium chlorhydrate (part of the complex), zirconium chlorhydrate, and glycine, and zirconium chlor-

hydrate and aluminum acetate all produced allergic granulomas. Since various combinations of the elements of the zirconium chlorhydrate, aluminum acetate and glycine complex result in a granulomatous response, the Panel, as noted earlier, has yet to receive adequate scientific evidence that zirconium chlorhydrate will not be liberated in the lung from the complex by the action of degradative enzymes within the alveolar macrophage.

(v) In tests where one manufacturer of a zirconium chlorhydrate, aluminum chlorhydrate aerosol antiperspirant (since withdrawn from sale) found toxic changes in the lungs of test monkeys, a parallel test with a product containing a complex of zirconium chlorhydrate, aluminum chlorhydrate, and glycine produced no such changes.

The test described was a routine toxicologic test, not one designed specifically to look for a tendency to produce granulomas over a prolonged period of time. As noted previously, standard 90-day tests would not be expected to reveal the kinds of changes the Panel is concerned about. Furthermore, the fact that the similar product did produce changes serious enough to provoke a voluntary product recall, suggests the existence of a narrow margin between safety and toxicity with inhaled zirconium particles. Again, should the complex product be broken down by alveolar macrophages, it is likely a complex similar to the one causing changes in the monkeys lungs would be liberated.

(c) Data Necessary to Prove Zirconium Spray Safe

Because millions of Americans have already used zirconium in antiperspirant aerosols, the Panel is concerned that the following safety information was unavailable.

(i) No data exist concerning the fate of zirconium antiperspirant complex once it gets to the lungs. Such animal tests could be done with present technology and would include: (a) analysis for zirconium compounds in animal lungs after specific periods of time (i.e., 90 days, 180 days, 360 days), (b) tests to see if zirconium is transported to the regional lymph nodes, (c) tests for zirconium in the liver, bones, other body organs as well as excreta.

(ii) No data exist to show the absence of a potential for zirconium-containing aerosols to produce pulmonary fibrosis after very prolonged use. Rodents should be exposed to lifetime inhalation tests. Beagle dogs and monkeys could be exposed to tests for periods of two years or more. Pulmonary function tests could be done on test animals and controls.

(iii) More sophisticated methods than those available to Epstein for assessing the immunologic hazards of marketed products now exist.

Specifically, techniques which have proven capable of inducing granuloma in animals should be applied to zirconium (Refs. 17 through 22). An animal species sensitive to the zirconium compounds which have been shown to react in man must be utilized. Both cutaneous and pulmonary allergic response to zirconium compounds should be produced. Prolonged exposure to zirconium compounds that have been found reactive in man should be used in various doses and time schedules. Because allergic responses sometimes are facilitated more by intermittent exposure of variable intensity than by continuous heavy exposure, lifetime observation of such sensitized animals to candidate zirconium compounds would be required in order to allow for the influence of changes with normal aging. Negative reactions with large numbers of animals in this kind of test would be highly desirable before inhalation of any zirconium compounds can be regarded as fully safe. Also it is now possible to remove white blood cells from persons known to be allergic to zirconium and to test those cells with different zirconium compounds and zirconium complexes. Such testing is done *in vitro* and does not require that human subjects be repeatedly skin tested and their immune resistance repeatedly challenged by potential sensitizers. Using such *in vitro* techniques, it can be expected that investigators will be able to perform much more extensive tests than can be done directly on patients (Ref. 22).

III. BENEFITS FROM ZIRCONIUM AEROSOL ANTIPERSPIRANTS

There is no available evidence that the addition of zirconium to the usual aluminum-containing antiperspirant has any unique benefit. The most that has been claimed for the zirconium-containing aerosol antiperspirants is that they are somewhat more effective in reducing underarm perspiration than comparable aerosols containing aluminum chlorhydrate as the active ingredient.

The differences, however, appear to be slight. Also, it appears that levels of perspiration control quite comparable to those achieved by the zirconium-containing aerosols can be achieved with zirconium creams, roll-ons or aluminum roll-ons or lotions—products totally lacking in potential for pulmonary toxicity.

IV. BENEFIT VERSUS RISK OF ZIRCONIUM AEROSOL ANTIPERSPIRANTS

In reviewing the benefit from the use of zirconium antiperspirant aerosols, it was pointed out that quite comparable, if not identical reductions in the amount of underarm perspiration may be achieved by products without zirconium's potential for producing serious lung disease.

Whether or not the ability to limit underarm perspiration is a matter of importance to the American public is not a question the Panel chooses to discuss here. The Panel is satisfied, however, that the American public believes that products sold for this purpose are of proven safety and would not knowingly assume even a modest risk of lung disease from their use.

Further complication of the use of these products comes from the fact that exposure to these aerosols when delivered from propellant aerosols cannot be confined solely to the individual user. These products are usually used in bathrooms which may be small and poorly ventilated and which are used by other members of the family within a time period while significant amounts of the product remain in the air. It has been estimated that more than 25 percent of the particles from aerosolized antiperspirant products are 3 microns or less. Particles in this size range would remain suspended in an unventilated room for hours (a 3 micron spherical particle of unit density would settle at a velocity of approximately 0.4 meters per hour).

At this point in time the analysis of benefit to risk considerations lead the Panel to feel that zirconium compounds should not be sold for use in aerosol antiperspirants until the questions raised about their safety are adequately answered.

A further question is whether the sale of these agents should be permitted pending resolution of these safety questions. Here again, benefit to risk considerations must be weighed. On the one hand are the slight to negligible increments of underarm perspiration control available to users of these products. On the other side is the chance of producing lung disease where the population at risk may approach 100 million. Should zirconium-containing aerosol antiperspirants turn out to carry a health hazard, the magnitude of the problem could be considerable. In this connection the Panel would note that tests of the sort suggested earlier in this statement have been feasible for several years and could have been done.

V. PLAN OF THE PANEL

The Panel feels this statement should be made known to all interested parties. The Panel will accept comment on this statement at an open meeting on December 16, 1974 at the Parklawn Building in Rockville, Maryland.

Mr. FOUNTAIN. Of significance, I think, is the following excerpt which appears at page 19:

There is no available evidence that the addition of zirconium to the usual aluminum-containing antiperspirant has any unique benefit * * *. Also, it appears that levels of perspiration control quite comparable to those achieved by the zirconium-containing aerosols can be achieved with zirconium creams, roll-ons or aluminum roll-ons or lotions—products totally lacking in potential for pulmonary toxicity.

At pages 20 and 21 the panel made the following statement:

At this point in time the analysis of benefit to risk considerations lead the panel to feel that zirconium compounds should not be sold for use in aerosol antiperspirants until the questions raised about their safety are adequately answered. * * *

On the one hand are the slight to negligible increments of underarm perspiration control available to users of these products. On the other side is the chance of producing lung disease where the population at risk may approach 100 million. Should zirconium-containing aerosol antiperspirants turn out to carry a health hazard, the magnitude of the problem could be considerable. In this connection the panel would note that tests of the sort suggested earlier in this statement have been feasible for several years and could have been done.

The panel held its seventh meeting on December 16 and 17, 1974, to hear the industry response to the panel's November 27, 1974, statement from which I quoted. The committee heard presentations by experts and industry representatives. I am inserting into the hearing

record the cover sheet and pages 35 and 36 of the minutes of the closed sessions of the meeting which state:

The panel made no decisions but wanted to take the time until the next meeting to review the data presented to them in light of their previous review and the presentations made at their October/November meeting.

[The information follows:]

SUMMARY MINUTES OF THE OTC PANEL ON ANTIPERSPIRANT DRUG PRODUCTS

[Seventh Meeting, December 16 and 17, 1974, Parklawn Building, Rockville, Md.]

Panel Members:
E. William Rosenberg, M.D., Chairman.
Zenoma Mally, M.D.
Charles Evans, M.D., Ph. D.
Jane Rosenzweig, M.D.
Eli Shefter, Ph. D.
Robert Scheuplein, Ph. D.
J. Wesley Clayton, Ph. D.

Liaison Members:
Consumer.—Ms. Marsha Gardner.
Industry.—Norman Estrin, Ph. D. (acting).

FDA Staff Members:
Mary K. Bruch, Executive Secretary—Division Anti-Infective Drug Products.
Michael Kennedy, Panel Administrator—OTC Staff (acting in absence of Lee Geismar).
Joe Hussion, Drug Information Analyst—OTC Staff.
Gary Yingling, General Counsel's Office.

CLOSED SESSIONS—DECEMBER 16–17, 1974

Brief closed sessions were held at the end of the open session on both days. Discussion of the material presented to the Panel, the importance of the data, apparent inconsistencies in data and design of the experiments were the major elements of discussion. The Panel made no decisions but wanted to take the time until the next meeting to review the data presented to them in light of their previous review and the presentations made at their October/November meeting.

(Prepared by: Mary K. Bruch, Executive Secretary.)

Mr. THOMPSON. In the November 27 report which you mentioned there is a statement where they said the advisory panel feels some zirconium-based chemicals produce skin irritations and other problems while others did not, at least on the basis of available information. They mentioned one complex, if that is the proper term, which consists of zirconium chlorhydrate, aluminum chlorhydrate, and glycine.

For the sake of the nonscientists, is it possible that one complex containing zirconium could produce difficulties and another complex containing zirconium could not?

Dr. SCHMIDT. That is a hypothetical question. The answer to that would be "yes."

Mr. THOMPSON. Are there any products which have shown a lesser degree of either external or internal irritation than, say, the product removed from the market voluntarily?

Dr. SCHMIDT. I am sorry that I cannot answer that. I do not have that information. Whether or not the panel has any sound information in that area which they will provide, I do not know at this point.

Mr. THOMPSON. Are you grading various zirconium compounds being developed?

Dr. SCHMIDT. It is my understanding that the panel has talked about this sort of thing and the types of studies that could be or should be done. I think sound experimentation could be done to get at the answer to the question.

Mr. GOLDHAMMER. I would like to attempt to get some clarification concerning those zirconyl complexes. In my review of the minutes I detected that there was considerable doubt about the knowledge of the composition of these complexes. As a matter of fact, there was some suggestion that perhaps the doubts about the composition were so great that there were questions as to whether the uniformity of the product could be guaranteed.

If a product's composition is not established precisely, and if there are doubts about the ability of the manufacturer to make a uniform product of the same composition, would that fact alone throw a drug into the category of new drug?

Mr. PINCO. That is such a hypothetical question in terms of scope that I do not feel that I could responsibly answer it. The difficulty we are getting into here, both with Mr. Thompson's questions and your question, are the specifics of this OTC review panel's work on ongoing processes.

While we can discuss the process, I think to discuss the specifics of any product or series of products or compounds would be highly improper for us at this stage because we do not have the report of the panel which we can discuss in detail at this moment. We have not received it nor reviewed it. I would have to beg off from that question at this time.

Mr. GOLDHAMMER. The Food and Drug Administration has its experts in chemistry, some of whom are highly qualified. Have your own biochemists and experts in the manufacture of drugs and in their control made their own independent appraisal of whether the composition of these complexes has been established?

I am talking about the zirconyl complex.

Mr. PINCO. I am not aware our Bureau of Drugs has conducted that type of in-depth review.

Dr. CROUT. No, because that stage of the process has not yet occurred.

Mr. PINCO. That would occur normally after we have received the report and evaluated internally as to what we may or may not wish to do with respect to it.

Mr. GOLDHAMMER. I got the impression that there were some doubts about whether or not the composition of the zirconyl complexes had been established. Are there such doubts?

Dr. SCHMIDT. What you are doing is pointing out one of the great values of the OTC review and the use of the experts on those panels. This is precisely their purpose. You have made a good point, and that is that this process is very helpful and very important. We will now be able to take whatever appropriate action is indicated by their report.

Mr. GOLDHAMMER. My question was whether there are such doubts.

Mr. PINCO. We cannot comment on that at this stage without receiving their report and review.

Mr. FOUNTAIN. Are there doubts by others, other than yourselves?

Mr. PINCO. If the report states that the panel has doubts, then apparently that is true. If it does not, then we would have no way of knowing. I think the minutes would have to speak for themselves, Mr. Chairman.

Mr. FOUNTAIN. The panel's eighth meeting was held on January 30 and 31, 1975. I am placing into the record the cover sheet and pages 19 and 20 of the minutes of that meeting which reflect the decisions reached.

[The information follows:]

SUMMARY MINUTES OF THE OTC PANEL ON ANTIPERSPIRANT DRUG PRODUCTS

[Eighth Meeting, January 30–31, 1975, Parklawn Building, Rockville, Md.]

Panel Members:
E. William Rosenberg, M.D., Chairman.
Zenona Mally, M.D.
Jane Rosenzweig, M.D.
Eli Shefter, Ph. D.
Robert Scheuplein, Ph. D.
J. Wesley Clayton, Ph. D.

Liaison Members:
Consumer.—Ms. Marsha Gardner.
Industry.—Robert Giovacchini, Ph. D.

FDA Staff Members:
Mary K. Bruch, Executive Secretary—Division Anti-Infective Drug Products.
Lee Geismar, Panel Administrator—OTC Division.
Joe Hussion, Drug Information Analyst—OTC Division.
Gary Yingling, General Counsel's Office.
Peter Hutt, General Counsel's Office.

Decisions reported herein are provisional in nature and may be modified or revised in subsequent meetings of the Panel or in their final complete report to the Commissioner.

Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Liaison Members, Consultants, or FDA Staff Members.

Adopted: March 25, 1975.

LEE GEISMAR,
for E. WILLIAM ROSENBERG, M.D.,
Chairman.

The OTC Antiperspirant Panel made the following decision: "All zirconium-containing aerosol antiperspirants/deodorants be placed in Category II."

Our decision was made for the following reasons:

1. Unnecessary incidence of bronchial and respiratory distress.
2. Unnecessary burden of zirconium particles on respiratory and gastrointestinal tract.
3. Likelihood of retention of zirconium particles in the lung.
4. Insufficient evidence that zirconium-containing particles in the body are not altered into substances of probable antigenicity.
5. Insufficient evidence of safety of long-term exposure to zirconium-containing aerosols.
6. Our assessment as to benefit-to-risk-ratio: Comparable degrees of respiration control are achievable with other preparations which are generally recognized as having less potential for harm.
7. The chemical and physical complexities of zirconium-containing antiperspirant formulations preclude its being identified in a generic manner and therefore each company's product should be evaluated separately. The Panel believes the IND/NDA procedure would be required to achieve this.

The Panel believes that the major risks associated with the products, discussed above, are primarily those of long-term use. We do not believe users of these products are in imminent danger, since, at this time, we do not have documented cases of serious clinical disease. We see no need to suggest a product recall.

The continued marketing of these products should be permitted contingent upon the vigorous pursuit of safety testing by industry. The Panel plans to provide guidelines for those tests it considers essential.

(Prepared by: Lee Geismar for Mary K. Bruch.)

Mr. FOUNTAIN. These pages indicate that the panel once again decided: "All zirconium-containing aerosol antiperspirants/deodorants be placed in category II."

Category II are those not generally recognized as safe. Is that right?

Dr. SCHMIDT. Yes, sir.

Mr. FOUNTAIN. Among the reasons listed for the decision are: "unnecessary incidence of bronchial and respiratory distress, unnecessary burden of zirconium particles on respiratory and gastrointestinal tract, likelihood of retention of zirconium particles in the lungs." On the benefit-to-risk ratio: "Comparable degrees of perspiration control are achievable with other preparations which are generally recognized as having less potential for harm."

At page 20 of the minutes the panel is reported to have indicated that it saw no need to suggest a product recall and that the continued marketing of these products could be permitted contingent upon the vigorous pursuit of safety testing by industry.

This recommendation appears to be inconsistent with the decision to place the zirconium aerosol antiperspirant in category II. I wonder whether you can enlighten us as to the implications of this recommendation. Does it mean that the panel is recommending that interstate shipments of these antiperspirants be permitted to continue, notwithstanding the fact that the panel did not recognize them to be safe?

Dr. SCHMIDT. I think at this point it would be wise for Mr. Hutt to review briefly the implications of category II and what process we invoke in that case.

Mr. HUTT. Mr. Chairman——

Mr. FOUNTAIN. That is a legal question and that is what you will answer.

Mr. HUTT. Yes.

The process set out in the regulations governing the OTC drug review which you have placed into the record includes several stages. The first stage is the panel's review and recommendations to the Commissioner. Those recommendations are then placed in the Federal Register as a proposed monograph with time for public comment. After the time for public comment the Commissioner publishes a tentative final monograph and provides an opportunity for any interested person to request an oral hearing before the Commissioner which, I might add, may not be delegated by him.

After that oral hearing, if one is justified, a final monograph is published. At that point, on the effective date of that final monograph, we implement the decision and recommendations all at one time according to the effective date set out in the monograph.

We are at the first stage with zirconium, not at the end stage. The issue we put, and which is still pending before the antiperspirant panel, can be broken down into several parts.

The first part is whether it is in category I, II or III. The second part is, if it is in category II, is that a decision which should be taken out of the normal process and implemented immediately or should it

be handled in the course of the normal process set out in the regulations and thus implemented when the final monograph is promulgated?

You must recall that part of due process of law is permitting people who are affected adversely by a decision to comment upon it and pursue their administrative and judicial remedies.

What these minutes state is that, as of that meeting, and I emphasize as of that meeting, the panel had concluded that there was not sufficient hazard they could determine to justify taking the zirconium aerosol issue out of the ordinary course of the administrative process and handle it on an expedited basis.

That, as you know, was not the end of the matter. We are uncertain at this moment exactly what will happen, but as of that moment that was their recommendation.

I would like to emphasize they were not saying that as of the final date of the monograph, if it were to be in category II, that it should stay on the market. That is not what that statement says.

Mr. FOUNTAIN. Then you are saying that that recommendation is not necessarily inconsistent with the decision to place the zirconium aerosol antiperspirants in category II?

Dr. SCHMIDT. Just a point I believe is important. It is really not a recommendation. What you have there are minutes of meetings. If one traces through minutes of meetings one finds many times a conclusion at one meeting which is reversed at the next meeting and reversed at the next meeting.

You are not dealing with recommendations but you are dealing with minutes of meetings. I do not have a recommendation from that panel yet.

Mr. FOUNTAIN. You are dealing with expressions of opinion at the time the members participate?

Dr. SCHMIDT. That is right.

Mr. HUTT. In any event, to answer the other question, Mr. Chairman, that is clearly not inconsistent with an interim conclusion eventually to recommend class II to the Commissioner. It was a conclusion expressed at that moment that they should not make an immediate recommendation of expedited action.

Mr. FOUNTAIN. The most recent meeting of the review panel, as you know, was held on March 24 and 25 of this year. As we learned earlier today, the minutes of that meeting have not been prepared. However, I am informed that at the termination of the meeting on March 25, 1975, the panel chairman, Dr. Rosenberg, wrote in longhand a two-paragraph statement of the panel's decision which he personally delivered to the Commissioner.

Is that correct, Doctor?

Dr. SCHMIDT. That is correct.

Mr. FOUNTAIN. I am placing in the record a copy of the doctor's statement which was obtained from FDA. I have been informed that this is not a copy of the statement delivered by the panel's chairman to the Commissioner but rather a longhand rewrite of the original by an FDA employee assigned to work with the panel. I shall read the panel's statement in full inasmuch as it is short.

and this is written in longhand—

> The antiperspirant panel,
> recommends to the Commissioner that he take action to withdraw all zirconium-containing aerosol antiperspirants from interstate commerce (unanimous vote).

The recommendation is based on the November 27, 1974 statement augmented by subsequent presentation and submissions, further review of additional literature, and a review of the types and extent of studies required to adequately demonstrate the safety of the zirconium-containing aerosol antiperspirants.

[The statement referred to follows:]

MARCH 25, 1975.

The Antiperspirant Panel recommends to the Commissioner that he take action to withdraw all zirconium-containing aerosol antiperspirants from Interstate Commerce. [Unanimous vote.]

The recommendation is based on the November 27, 1974 statement augmented by subsequent presentations and submissions, further review of additional literature, and a review of the types and extent of studies required to adequately demonstrate the safety of the zirconium-containing aerosol antiperspirants.

Mr. FOUNTAIN. This now brings us up to date on the panel's review of this matter and its decisions.

It is my understanding that FDA has asked the panel to prepare a report to back up its decision and that the panel will meet, probably tomorrow and Friday, to consider and finalize its report to the Commissioner. Is that correct?

Dr. SCHMIDT. Yes, sir.

Mr. FOUNTAIN. Since the background has now been adequately developed, I yield to Mr. Thompson, if he has questions at this time.

Mr. THOMPSON. I would like to go back to the minutes of the January 30–31, 1975, meeting and enter the statement the chairman just read from the March 25 meeting.

I quote from the bottom of page 19 and the top of page 20 from those minutes of the January meeting in which the minutes state:

We do not believe users of these products are in imminent danger since at this time we do not have documented cases of serious clinical studies.

In the March statement which the chairman read, there is no support to back the recommendation. The recommendation is made, period, and as you stated, Mr. Hutt, that is almost a hypothetical recommendation until it goes through the complete process.

I wonder whether you would comment within the limits of the restraints you have stated, on the blanket nature of the March recommendation in that it deals with all products which are zirconium based, in light of the fact that some information seems to indicate there is a distinction according to the zirconium-based complex? Also comment on whether the FDA would examine individual products which I believe is the recommendation the panel made in one of its earlier sessions.

Dr. SCHMIDT. The panel dealt with a wide variety of experimental data of varying quality. They evaluated this data and they interpreted the data, went through a process of reasoning, and came out with conclusions.

I have two principal concerns always when the agency takes an action. One is for the quality of the evidence upon which conclusions are based. The other is the due process we followed.

We have asked the panel to lay out all of these issues, to lay out not just their conclusions but to lay out the evidence on which they base the conclusions and their reasoning by which they went with regard to the evidence.

I understand some of the issues you are now asking about are involved in what was just quoted, subsequent presentations, submissions,

further review, and so on, which I charged them to deliver to me in organized fashion on March 25.

Until I see that and look at that, I am unable to say anything more.

Mr. THOMPSON. After the November report which has also been referred to, and at the January meeting, in the minutes provided the subcommittee, it was stated in the minutes of February 4, 1975:

> The chemical and physical complexity of zirconium-containing formulations preclude its being identified in a generic manner, and therefore each product should be evaluated separately.

Recognizing again what you have just said in your own qualifications, is that a likely option which the FDA will be able to proceed upon?

Dr. SCHMIDT. Again, I really do not have any evidence before me which would make possible a reasonable statement by me. Certainly, what you now have is the best possible information and that is the minutes of an expert group.

Mr. THOMPSON. Thank you, Mr. Chairman.

Mr. FOUNTAIN. I am a little confused, Dector. I think what you are requesting is a logical thing. However, as I recall it, and I believe the record will back me up, during our hearings on propranolol, you stated that you were not concerned with the details relating to the advisory committee's discussions and reasoning, but were concerned primarily with the panel's recommendations. How do you reconcile those two statements?

Dr. SCHMIDT. That is really very simple. I said a few moments ago that when one reads the minutes of meetings of a group one can find that at one meeting they feel this way and then they may hear additional evidence, they may do some reading, and they may change their minds later. I said at that time that I make my decisions based upon what I said just a few moments ago.

The final report of the group, when they have completed their investigation and discussion, tested their theses and find some wanting and some quite firm, then they render a report. Then at that time, I ask them to lay out not just their conclusions but to lay out their evidence and their reasoning behind those conclusions in the final report.

I am not interested in the details that take place during the process of evolving what I must have at the end, which is the evidence, rationale, and conclusions. Therefore, in no way are these statements of mine inconsistent or illogical.

Mr. FOUNTAIN. Did you require this kind of detailed report in connection with propranolol?

Dr. SCHMIDT. Yes, sir. When we take an action——

Mr. FOUNTAIN. Before you made a decision?

Mr. HUTT. No; we did not.

Dr. SCHMIDT [continuing]. I may not be sure of what action you are talking about.

Mr. FOUNTAIN. There was no report. Is that right?

Mr. HUTT. Mr. Chairman, there was no report at that time. One of the things we have done in the OTC drug review, obviously, is to build on our past experience. We do recognize the need for detailed reports at this time and are improving across the board on all of this.

Probably the most detailed reports we have ever required have been in the OTC drug review. I doubt we could ever meet the standard of the OTC drug review in any of the prescription drug areas because it is quite a different process.

Mr. FOUNTAIN. Doctor, even though the March 25, 1975, statement by the chairman of the panel, backed by a unanimous vote, clearly recommends to you that action be taken to withdraw all zirconium-containing aerosol antiperspirants from interstate commerce, you still want, in addition, a report on the basis upon which they made this recommendation. Is that what I understand you to be saying?

Dr. SCHMIDT. Absolutely.

Mr. THOMPSON. And more detail?

Dr. SCHMIDT. I must have the reasoning and the evidence behind the recommendation.

Mr. GOLDHAMMER. Mr. Hutt, you indicated you are constantly improving your handling of the advisory committees.

Mr. HUTT. Hopefully.

Mr. GOLDHAMMER. However, in your January 1972 proposed regulations setting up the OTC panel's review and the monographs, those proposed regulations, and the approved and finalized regulations in May of 1972, provided for these reports.

I believe that the propranolol, the DES, and the Depo Provera matters were handled after the May 1972 publication of your OTC review regulations. However, there were no reports in any of these cases; there was simply a vote. There was an executive secretary of the advisory committee there and minutes were prepared. Aside from that, there was no request for a formal report in any of these instances.

Dr. CROUT. I agree with that. The OTC panel system was begun in a formalized way and with a relatively stylized mission. Each one of those panels is to produce a report, and the process for doing this was well thought out ahead of time, and it is in the regulations.

The other advisory committee system which we operate in the Bureau of Drugs began substantially more informally, had many more developmental problems, considered different issues at each meeting, and there is no question that in its earlier days had problems with identifying exactly what were the recommendations of the committee. That has been a recognized flaw and has been corrected by the procedural regulations which will be out next month.

We are going to a system of requiring all of those committees' recommendations be in the form of written reports. The written report may be separate from the minutes or it may be included in the minutes. However, that is the purpose of solving the precise problem.

Mr. FOUNTAIN. As I understand it, you have not made a firm decision as to what to do about zirconium aerosol antiperspirants. Is the reason you have not done so because you are awaiting this report?

Mr. HUTT. That is correct.

Mr. FOUNTAIN. Is the crux of the matter the question of whether zirconyl aerosols are generally recognized as safe among qualified experts?

Mr. HUTT. Yes, sir.

Mr. FOUNTAIN. Is the phrase "not generally recognized as safe" synonymous with the phrase "found to be unsafe"?

Mr. HUTT. I would say no, Mr. Chairman.

Mr. FOUNTAIN. In other words, if a drug is not generally recognized as safe by qualified experts, that does not necessarily mean that the drug has been found to be unsafe?

Mr. HUTT. No. The phrase "general recognition of safety" is not synonymous with safety, with proof of safety. You can have proof of safety and not general recognition of safety. The statute recognizes that distinction itself.

Mr. FOUNTAIN. I think we understand that. I wanted that explanation in the record.

In other words, we can have a situation where a drug may be quite safe, but where the safety has not yet gained general recognition among the qualified experts.

Mr. HUTT. Yes, sir.

Mr. FOUNTAIN. A lack of recognition of safety may be due to the fact that sufficient information concerning the action of the drug, or its composition, is not available. Is that a correct statement?

Mr. HUTT. Yes, sir. The Supreme Court has particularly pointed out in one of the cases it handed down in June of 1973 that general recognition of safety must ordinarily, and I emphasize "ordinarily," be based upon widely available published literature. That is carried over in our OTC drug regulations.

Mr. FOUNTAIN. Under those circumstances, the law requires that a new drug application must be filed with and approved by FDA for that drug if it is to be legally shipped in interstate commerce. Is that right?

Mr. HUTT. Yes, sir.

Mr. FOUNTAIN. On June 10, 1970, the subcommittee held a hearing on cyclamate sweeteners at which Mr. Goodrich, then FDA's General Counsel, appeared as a witness. He was questioned on the legal construction of the term "not generally recognized as safe." He said at page 10 of that hearing:

> We are still involved, Mr. Chairman, in a good deal of litigation over the exact meaning of that term, both from the standpoint of the new drug law and food additives. But the cases we have so far—and I think they are mostly good, because we won most of them—are that where there is genuine difference of opinion among responsible experts, the product cannot be generally recognized as safe.

Do you agree with Mr. Goodrich's interpretation?

Mr. HUTT. Indeed I do.

Mr. FOUNTAIN. Mr. Goodrich added:

> A product can only be generally recognized as safe, say some of the courts, if there is in the open literature a source of data to which experts could turn to determine whether or not the product has been tested adequately and shown to be safe.

Would you agree with that?

Mr. HUTT. I would, Mr. Chairman, and since then the Supreme Court has affirmed that position. That position appears in our regulations.

Mr. FOUNTAIN. With respect to zirconyl aerosols, is there a source of data to which experts can turn to determine whether or not zirconyl aerosols have been tested adequately and shown to be safe?

Mr. HUTT. That is one of the issues before the panel, Mr. Chairman. We could not comment on that at this time. That gets into the substance of whatever recommendations they may or may not be making.

Mr. FOUNTAIN. Does FDA have such source of information at its disposal?

Mr. HUTT. I am not sure any of us have ever looked into that issue.

Dr. CROUT. Not independently of the OTC review because that is what the OTC review was set up for. Any information which we have in our files on an OTC product we attempt to see is submitted to an OTC panel.

The OTC review is meant to be the focal point for the review of all issues concerned with OTC drugs.

Mr. FOUNTAIN. Of course, you have already testified that no NDA ever has been filed, so you do not have information in support of that.

Dr. CROUT. We have toxicological data given to us by Gillette, but that has been given to the panel. They are evaluating that as part of their total information.

Mr. FOUNTAIN. As I review the record and the minutes, and I appreciate your request for details in support of the recommendation, it appears they have three times recommended that this be withdrawn.

Dr. SCHMIDT. No.

Mr. HUTT. They have tentatively categorized it category II. That is correct, Mr. Fountain. They have not recommended it be withdrawn. They have come up with a tentative conclusion which may be in subsequent recommendations.

Mr. FOUNTAIN. They did recommend that in the letter which was hand delivered to you, did they not?

Dr. SCHMIDT. Yes, sir. However, the second paragraph of that is important. The second paragraph cites that the recommendation is based on the November statement augmented by a number of things. Part of what it was augmented by was their discussion held just prior to the chairman's coming up to see me. I cannot base my actions on squishy oral reports.

Mr. HUTT. Mr. Chairman, the chairman of the panel, Dr. Rosenberg, fully agreed with the need for a report. He simply wished the Commissioner to know that the report would be forthcoming. That was not an issue.

Mr. FUQUA. There was never a formal decision made by the panel?

Dr. SCHMIDT. The formal decision was made by the panel on that date, which was March 25. The substance of their decision was conveyed to me. They said this would be followed by the information which I required.

Mr. FUQUA. This is the report they gave you, then?

Dr. SCHMIDT. Yes.

Mr. FOUNTAIN. Before you arrived, Mr. Fuqua, Dr. Schmidt had stated, notwithstanding that, he wanted a full report giving the reasons for their recommendation and all of the evidence, the literature, and so forth, which they had examined in support of that recommendation.

Mr. FUQUA. Thank you. That seems reasonable from this hand-written report.

Mr. GOLDHAMMER. If I may clarify a point.

Mr. FOUNTAIN. Yes, Mr. Goldhammer.

Mr. GOLDHAMMER. Mr. Hutt, you agree with Mr. Goodrich that all you have to do is to establish a substantial difference of opinion, and if there is not——

Mr. HUTT. Yes.

Mr. GOLDHAMMER. Let me finish. If there is not in the literature sufficient information to establish safety, or if the test data is not available to establish safety, then the experts are justified in saying, "I just can't recognize it as safe." It may be absolutely safe, but the information is not available upon which they can make such a decision; therefore, they do not recognize it as safe.

That is a fair statement to make, is it not, Dr. Crout? If you do not have the information it may be safe then you cannot recognize it as safe. Is that right?

Dr. SCHMIDT. This is what the panel is for.

Mr. GOLDHAMMER. If I may continue. I want the record to show my reasoning. The panel has indicated on three occasions that there is no recognition of safety among the qualified experts, and in November they published a report where they specified why they came to that conclusion. Why do you need another report? Is it not enough for them to tell you that there is not enough information around upon which they can make a determination, and, therefore, it is not generally recognized as safe?

Mr. HUTT. No.

Dr. SCHMIDT. The answer is no. I would read from page 21 of that report:

> The panel feels this statement should be made known to all interested parties. The panel will accept comment on this statement at an open meeting on December 16, 1974, at the Parklawn Building, Rockville, Md.

The purpose of this statement was to invite comment on their position at that time.

Mr. HUTT. Mr. Goldhammer, on top of that, the question of difference of opinion is a very tricky one in litigation. We have never had a court case in which any court has accepted an expert going on the witness stand and saying, "I do not think this is generally recognized as safe" and then shutting up and saying nothing further. He has always given the reasons. He has pointed out the lack of literature, or the specific literature and has discussed the problem.

In short, on the stand, in testimony, he has given the very kind of report we are asking for here. So the answer to your question of whether it is enough simply to say there is a difference of opinion is that it is not enough. There must be a scientific basis for that difference of opinion, and if there is, then that is quite sufficient. I would agree with that.

Mr. GOLDHAMMER. Dr. Schmidt, it is true, is it not, that they heard additional data from the manufacturer after the November report of the review panel. And in January, after considering that, they said nothing new has been given to them; it is still category II. Is that not correct?

Dr. SCHMIDT. Well, that was in their minutes, but——

Mr. GOLDHAMMER. Were the minutes inaccurate?

Dr. SCHMIDT. No; I said it was in their minutes but it is not a report to me.

Mr. GOLDHAMMER. You have the minutes available. This is an official document filed with FDA?

Dr. SCHMIDT. Yes.

Mr. HUTT. We are back into the middle of the process issue. The question you are apparently raising is: Should we, whenever any of the 17 panels in the midst of its deliberations come up with an interim conclusion in its minutes that something should be placed in category II, take that out from the panel, expedite it, immediately go ahead and implement it? The answer is no, unless there is a recommendation by the panel to expedite it for good sound reasons.

Mr. FOUNTAIN. We shall pursue this further.

Mr. FUQUA. It would seem to me that, based on this as a recommendation to the Commissioner, you would have to defend any position that the Commissioner would take in removing a product from the market in what could develop into litigation by whomever was involved. Is that not true?

Mr. HUTT. Yes, sir.

Mr. FUQUA. As you pointed out you would have to justify to a judge in an injunctive proceeding the reason the Commissioner took those actions. Is that not correct?

Mr. HUTT. Yes, that would be true for direct court action or when going through a proposed regulation. However, it would be the same thing ultimately.

Mr. FUQUA. You still would have to justify what you did and you would need information from expert panels because this is a topic requiring technical expertise. You would need some type of information to support whatever you did.

Mr. HUTT. Without question.

Mr. FUQUA. Could you tell me the makeup of the panel? I assumed some pathologists or dermatologists were present? What was the professional makeup; not necessarily the names?

Mr. HUTT. We have that information. There was an attempt in this panel, as in all panels, to have a variety of different medical disciplines.

Mr. FUQUA. It is my understanding you are dealing with an antiperspirant. This would deal with a rash and other types of effects. I assume you would need a dermatologist on there. I understand one of the points made was not the rash but some inflammation which developed in the lungs of monkeys. Is this right?

Mr. HUTT. We have a toxicologist who was on the committee. We could provide for the record the curriculum vitae of each of the seven members of the panel. There is another important point. The panel consists of all M.D.'s, Ph. D. combinations, or one Ph. D., in all fields. In addition, the panel sought out experts in pulmonariasis, inhalation toxicology, and so on, from all around the world. They did gather the world's expertise in this area and had the input of those experts.

Mr. FUQUA. Regarding the point in question?

Mr. HUTT. Yes. I would suggest, Mr. Fuqua, we submit for the record at least a brief curriculum vitae not only of the panel members but of the outside experts who came in and participated at the one particular meeting.

Mr. FUQUA. That would be very helpful.

Thank you, Mr. Chairman.

[The curriculums vitae referred to may be found in the appendix at pp. 293–309. No curriculums vitae of the outside experts referred to were submitted by FDA.]

Mr. FOUNTAIN. As I understand it, if it is a new drug, all you have to establish to the court is that it is not generally recognized as safe.

Mr. HUTT. Mr. Chairman, the Government has the burden of proof of establishing it is a new drug.

Mr. FOUNTAIN. Right.

Mr. HUTT. That would require us to prove the various things to which Mr. Goldhammer earlier made reference. We have the burden of proof of establishing that in court.

Mr. FOUNTAIN. Mr. Goodrich also testified, and I quote from page 10 of the June 10, 1970, hearing:

> The criteria I would apply from a legal standpoint is that if there were a responsible scientific opinion contrary to the belief in safety that that could not be generally recognized as safe, even though the vast majority may believe the product safe. * * * This is the kind of thing that was involved in some of our litigation. * * *

Do you agree with that opinion?

Mr. HUTT. I might take one slight disagreement. If, for example, one person testified one way and 10 the other way—we have never had one of those cases and Mr. Goodrich was not saying that we did—then it might well be that you could conclude it was generally recognized as safe.

What he was referring to was the normal case where we have either a clear 50–50 division of opinion or something close to that. Certainly wherever you have a substantial body of opinion on both sides, then it would not be generally recognized as safe, again assuming that those who say it is not recognized as safe give good, sound scientific reasoning for their position.

Mr. FOUNTAIN. I think the hearing record should reflect how FDA proved in court that a given drug was not generally recognized as safe or effective among qualified experts. I believe the "not-generally-recognized-as-safe" concept is now pretty well established by court decisions; is it not?

Mr. HUTT. Yes. There are still some different court opinions but I believe it is fair to say that the method by which we go about establishing that is fairly well known.

Mr. FOUNTAIN. In fact, the courts apparently are not reluctant to study cases involving new drug charges on the basis of affidavits alone, without testimony from witnesses.

Mr. HUTT. That depends on the court. Some are reluctant and some are not.

Mr. FOUNTAIN. A case in point is the "Trim Cigarette" case, with which you may be familiar.

Mr. HUTT. That is a very, very old case. It was probably the first general recognition-of-safety case.

Mr. FOUNTAIN. A more recent one is the Second Circuit Court of Appeals February 1968 decision in the AMP case, which affirmed the summary judgment of the lower court declaring AMP's ligatures and inserting instruments to be new drugs. That case turned, in part, as I understand it, on whether AMP's products were generally recognized as safe. As you know, each side submitted an expert's affidavit. The

expert for the Government was Dr. William J. Gyarfus, a medical officer in FDA's Bureau of Drugs. He expressed his judgment that the ligatures were not generally recognized as safe since they remain implanted in the body and long-term toxicity studies would be required.

AMP submitted an affidavit of a professor of surgery and chairman of the department at the Medical College of South Carolina, who attested to his experience and studies of the AMP ligatures and ligating instruments and expressed his view that they were safe.

The court in that case observed, and I quote:

> On the basis of those two affidavits we must conclude that AMP's products are not generally recognized among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof and are therefore new drugs within the meaning of section 201(p) of the act. This is, we think, an appropriate case for summary judgment.

Are you familiar with that case? Do you agree with the court's interpretation?

Mr. HUTT. I agree with the court's interpretation there. The difficulty we have had, Mr. Chairman, is that other courts have gone the other way. They have said affidavits are not sufficient for summary judgment and have required a full trial with many witnesses and experts, even on trivial products.

Mr. FOUNTAIN. This was a court of appeals.

Mr. HUTT. Yes, but that does not mean every district court in the country will see the matter the same way.

Mr. FOUNTAIN. Are you waiting for every district court in the country to see things the same way before you make a decision?

Mr. HUTT. No. We go ahead frequently, but it means that when the district court refuses to go along with us we have a major important piece of litigation which may take a year to conclude. This happened, for example, when we seized Excedrin PM as a new drug. We asked for summary judgment. We got turned down. The case still has not gone to trial. That was over 4 years ago.

Mr. FOUNTAIN. As you probably recall, AMP contended, and again I quote from the decision:

> The defendant's motion for summary judgment should not have been granted because there remained an issue as to the safety and efficacy of AMP's products.

The court of appeals answered that contention by declaring:

> The safety of the product is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education, and Welfare for a determination as to safety, adequacy of testing, and so forth.

Do you agree with that?

Mr. HUTT. Again, I agree with all you are saying because you are quoting from cases favorable to the Food and Drug Administration. I should point out you are not quoting from cases which have gone the other way.

Mr. FOUNTAIN. How many have gone the other way?

Mr. HUTT. I could not give you——

Mr. FOUNTAIN. Can you give us some estimate for the record?

Mr. GOLDHAMMER. Name one.

Mr. HUTT. The Excedrin PM case is a clear one. The issue is not whether I agree as a lawyer with what you have said, or, indeed, whether certain courts of appeal have said that. When we are in a district court and it rules against us and holds we must have a trial, we cannot at that time take an interlocutory appeal to the U.S. court of appeals. We must litigate that case in that district court.

On top of that, I am sure you realize that in many of the trivial cases we have had—for example, one brought against a product called Vice Spice, a fake aphrodisiac—containing paprika, where we had to get affidavits from the chairman of the department of pharmacology at Michigan Medical School—it is very difficult to go to busy, important people to get an affidavit of that kind.

We have brought cases against hangover remedies, products such as Xerac Acne Gel—certainly not the most important cases. On each occasion we have had to go out and get a number of affidavits from busy and important people. On some occasions we have been unable to convince them to take their time to do that. These are terribly time-consuming pieces of litigation, which is why we pursued the OTC drug review rather than continuing what was a formidable and, indeed, impossible task on a case-by-case basis.

Mr. FOUNTAIN. I can appreciate the point of view you express and that it may not be important what your personal opinion is, except as it results in a decision by the Commissioner. However, you do not always have to await court action before you reach a decision on the basis of the law that certain actions should be taken by FDA. You are not saying you await court decisions to make a decision yourself.

Mr. HUTT. I am sorry. We bring those cases. What I am saying is that our resources are limited. As we told the Supreme Court, we could bring no more than at most perhaps 10, or at the maximum, 15 of those cases per year, contrasted with the 200,000 over-the-counter drug products on the market today. There is no way we could ever catch up with those by litigation.

Moreover, there is an even more serious problem. In our Xerac Acne Gel case, we won on the basis of affidavits in the district court. When we got to the U.S. court of appeals, the company informed us, at the point of time when we were briefing that case in the court of appeals, that they had changed the formula.

This would have meant that even if we had won the case in the court of appeals, which I assume we would have done, they would have had a new product back on the market and we would have had to start another seizure action. That could keep up through all eternity. Thus, the individual case-by-case approach is literally useless in the real world.

This is why we gave up on what was a very ineffective means of enforcement, a means which was not only ineffective in terms of actual results but using a great amount of our resources. We went, instead, to a highly effective means of rulemaking, namely, the OTC drug review.

Mr. GOLDHAMMER. You said there are over 200,000 OTC products on the market. I do not dispute that figure of 200,000.

You said if you tackled them all on a case-by-case basis you would be bogged down. I would agree with that if all those products were violative. However, are they all violative?

Mr. HUTT. We are finding, in terms of proper labeling as well as general recognition of safety and effectiveness, that every over-the-counter drug product in this country will be affected by the OTC review.

In that sense one can say they are all technically in violation of what good, modern medical science thinks should be proper indications for use, warnings against misuse, formulations, dosage regimens, and so forth.

If we were to go about reformulating and relabeling all over-the-counter drug products in the country on the basis of litigation alone, it could not be done. We would all have to agree with that.

If we do it by rulemaking, on the other hand, it is a feasible job.

Mr. GOLDHAMMER. On the other hand, many of these products have been on the market 30 to 40 years and longer. I am certain the Food and Drug Administration was aware of the more important ones, knew the labeling, had considered the labeling, and made certain decisions about whether or not action was indicated.

Let's take the antacid panel; that is the only one where you have a final order. Will you identify one antacid product which was dangerous to health in a real sense prior to the issuance of the monograph?

Mr. HUTT. I doubt I could give you one which was dangerous to health, although there was one combination which was concluded to be a possible health hazard. I forget what the combination was.

Mr. GOLDHAMMER. Was that a product which was put on the market after either 1938 or 1962?

Mr. HUTT. I would have to go back to the record. I must confess I have not looked at that monograph in some time.

The point is that the OTC review is not directed just toward outright health hazards but toward applying the most modern medical and scientific knowledge to upgrade all over-the-counter drugs, in terms of safety, effectiveness, and labeling.

I think it is very successful. The antacid monograph certainly affected every antacid product. Every single one has had to be reformulated or relabeled.

Mr. GOLDHAMMER. We have to put it in perspective. These 200,000 products are on the market and you contend you cannot tackle them on a case-by-case basis. Some of these products have been on the market for one-half century. The Food and Drug Administration apparently made up its mind that whatever was wrong with these products was not bad enough to do anything about. I don't see that you will change the situation any; you still will have to make up your minds as to whether you want to proceed on a case-by-case basis because of minor variations from the monograph.

Mr. HUTT. I do not agree with that. Once we have the monographs we now have a court decision in the National Nutritional Food Association case in the second circuit which states that our regulations are substantive. If appropriate, we can utilize that decision and can exercise summary judgment because we have engaged in substantive rulemaking.

The difficulty with the case-by-case approach, not having engaged in substantive rulemaking, is that you sometimes can get a court on the basis of a lot of affidavits to issue a summary judgment order, but many times you cannot. In any event, you have to get the affidavits.

Once you have a substantive rule you put the rule and the data behind it on the desk of the judge and move for summary judgment with nothing else. That is on a case-by-case——

Mr. GOLDHAMMER. That is on a case-by-case basis?

Mr. HUTT. No question. The difficulty is minuscule compared to the other approach.

Mr. GOLDHAMMER. If there are at that time 200,000 products out on the market which deviated in some significant way you would have to proceed against 200,000 products, would you not?

Mr. HUTT. The answer is yes, we would. However, what we are finding with the antacid monograph is having clear rules in the Federal Register, having done it so that there is no competitive inequity, so that all competing products are affected in the same way on the same day, then there is compliance or where there is not compliance, it will be of such a relatively small nature we will be able easily to pursue the enforcement procedure I just outlined.

Dr. SCHMIDT. That is the important point. We are establishing a standard which will be followed in most instances clearly by the industry. The standard will give us a basis of taking an action.

Another important point is that as a physician I have been concerned about several things. One is that self-medication is a very important part of our health care system. The OTC review is directed importantly against any unsafe products on the market. As you pointed out, some of these products have been around a long time. I would think any substantial safety problem would surface.

Many of the products are fairly recent, such as aerosolized antiperspirants, so your generalizations are, like most, not universally true.

I have been very concerned about the number of products on the market which are essentially totally ineffective. It seems to me again that it is good and it is desirable that drug products on the market be safe and effective for the purposes claimed, and that last bit is an important part of the OTC review.

I would not hazard a guess as to the number of products which are totally worthless which are on the market, but I think one of the effects of the OTC review will be that products which are out there will be not only safe but effective for the purposes claimed and will be fully and informatively labeled and that people will for once know what they are doing and will stop wasting their money often on worthless products.

Mr. HUTT. I did find the one example that I had recalled. It was a combination of an antacid with an anticholinergic. The conclusion was that the amount of an anticholinergic necessary to make it effective would make it far too toxic. The panel was terribly concerned about that.

This is a good example, also, of the way industry has reacted even before the report became available in the Federal Register. The manufacturer came in and said he was removing the anticholinergic immediately, before it had even gone through the entire administrative process.

Mr. GOLDHAMMER. Does that not occur often when you write a letter to a firm saying its product appears to be in violation, or after you have gotten a favorable court decision in a case? You then attack the violation on an industrywide basis and the industry gets the

message from having lost a case. Don't they generally all fall in line and you are not required to proceed against the whole class of products on an individual case-by-case basis?

Mr. HUTT. Our experience with the hangover remedies demonstrates that is not true.

Mr. GOLDHAMMER. Perhaps not always.

Mr. HUTT. We have brought case after case and have gotten absolutely nowhere. Indeed, there is nothing to prevent the same companies from putting out a totally different formulation as a new hangover remedy after having lost the case on the last formulation.

I would again point out that Xerac Acne Gel case. They did not await the court of appeal's decision before they put a new product on the market.

Mr. GOLDHAMMER. I will grant you there are times when it takes a long time for a message to sink in and corrections may be delayed. On the other hand, there are also perhaps an equal number of times when the message does sink in that the court has expressed its legal interpretation of a set of facts. You can notify the entire industry then that henceforth products bearing this kind of labeling will be proceeded against. That approach has been successful in instances, has it not?

Mr. HUTT. I am trying to think of one. Except in clear situations, where we have used Federal Register notices, I am not aware of any where that has been sufficient.

Mr. GOLDHAMMER. How about phenacetin? Have you not gotten out a regulation on that?

Mr. HUTT. Exactly.

Mr. GOLDHAMMER. Without a monograph?

Mr. HUTT. Where we have done it on a case-by-case litigation approach, we have had an enormous lack of success. One can look at the wrinkle remover cases. Companies still are putting out wrinkle removers. We can never catch up with all of those.

We had the hangover cases. We have a wide variety of other situations where we have brought individual cases, and the rest of the industry said they will go right on with what they are doing; FDA will have to catch up.

That is why we have abandoned that approach as the major way of law enforcement and gone to the rulemaking approach which is far more effective.

Mr. THOMPSON. To try to summarize, your monograph system is basically an attempt to broaden your authority and expedite the FDA's proceeding against products they think are in violation of the monographs. Is that correct?

Mr. HUTT. Yes.

Mr. THOMPSON. But the monographs do not preclude you from proceeding in previous lines of litigation against products. Is that correct?

Mr. HUTT. That is correct. In fact, we have two areas where we continue to bring case-by-case litigation. Anything involving a health hazard we will take up even though it is also going through the OTC drug review and handle that on an immediate basis.

A good example of that is the high dosage of vitamin A and vitamin D which we took out of the OTC review and handled in a separate

regulation in the Federal Register. That has now been appealed to the courts. That matter also is pending before the OTC review.

There is also patent fraud. Where it is a cancer quack or something of that kind, we will take action without awaiting the OTC drug review.

We have taken hexachlorophene out of turn. There have been a number of different products and ingredients we have taken where we have been concerned about a health hazard.

Mr. THOMPSON. Is it an accurate characterization to say the monograph system has broadened your capacity to deal with Dr. Schmidt's concern about products on the market?

Mr. HUTT. We believe so.

Mr. FOUNTAIN. I appreciate your saying one court may do one thing and another court may do something else. However, if I understand the AMP decision, you do not have to produce any evidence to establish the safety or effectiveness of a drug, but only that there is no general recognition of safety or effectiveness. Is that not right?

Mr. HUTT. I agree, Mr. Fountain. The question is whether you can do that by affidavits or testimony.

Mr. FOUNTAIN. You do not have to prove it is safe or effective?

Mr. HUTT. Yes.

Mr. FOUNTAIN. I think we may assume, with regard to the antiperspirant panel, that the members are qualified experts for safety evaluation of antiperspirant products, inasmuch as your May 11, 1972, notice relating to this states, "the individuals selected for panel membership are leading experts in the therapeutic category that the panel is reviewing."

Are they the type of qualified experts described in the statutory definition of new drugs: that is, in section 201(p) of the Federal Food, Drug, and Cosmetic Act?

Mr. HUTT. They were chosen precisely for that purpose.

Mr. FOUNTAIN. You would accept their safety and efficacy statements as scientifically and medically valid?

Dr. SCHMIDT. Yes. That is why I am awaiting their early recommendation to me.

Mr. FOUNTAIN. Would you accept their findings and opinions as representing the consensus of current and competent scientific and medical thinking on the subject matters referred to them for evaluation?

Dr. SCHMIDT. Not necessarily and not as you stated it. I will not accept very many people's unsupported conclusions. I have said several times what I require from them, which is their conclusions, and then both the evidence and the reasoning from that evidence which led them to those conclusions, because I believe as Commissioner of Food and Drugs I must make an independent assessment of this. This is my job, and I will carry out my responsibilities.

Mr. FOUNTAIN. Mr. Goldhammer has reminded me that you might not have appreciated the emphasis where I meant it to be. I asked whether you would accept their findings and opinions as representing the consensus of current and scientific medical thinking on the subject matter.

Dr. SCHMIDT. I said no. However, I qualified the no. I said no to the wording of your statement.

Mr. FOUNTAIN. And you object to the word "consensus"?

Dr. SCHMIDT. I think there is rarely a unanimous opinion among experts, and the more expert a group is, the less apt there is to be a unanimous opinion.

Mr. FOUNTAIN. Mr. Hutt.

Mr. HUTT. I would have to say that one could not accept, as I have said before, and present to a court a bareboned recommendation without being able to back it up with good, sound scientific reasoning.

Mr. FOUNTAIN. You keep responding by saying what you would have to submit to a court. I am asking you what you would accept.

Dr. SCHMIDT. Mr. Fountain, I think what is relevant to me is not what one judge as opposed to another judge may or may not accept as evidence of a disagreement among experts. What is important as far as this action goes, is what I will and will not accept.

Mr. Hutt has said that one judge might well have accepted one affidavit from each of two people unsupported by any scientific reasoning, and said "there is not general recognition of safety."

He also said that other judges will not accept one affidavit. The judge said "I don't think it is safe." He requires the laying out of scientific evidence for that person's not being willing to accept it as safe.

If we are going to talk about one judge or another, I am siding with judges who require evidence to be laid out.

Mr. FOUNTAIN. I think that is an appropriate way to reach a conclusion. Sometimes you make administrative decisions before you get to court.

Mr. HUTT. Mr. Chairman, let me emphasize one thing. If you are asking whether, based upon a good sound scientific reasoning we would accept these people as experts and their opinions as sufficient to back up a decision to go to court on the ground that these products are not generally recognized as safe and effective, the answer is a clear yes. There is no question about that.

Mr. FOUNTAIN. Do your instructions to these panels include the information that whatever their recommendations are, they must take into account the fact that you may have to go to court and prove it?

Mr. HUTT. Absolutely. Indeed I have become very unpopular with all of the OTC drug panels for constantly pushing them very, very hard for a clear statement of their scientific reasoning. I have said over and over again I have no interest in which way they come out on any issue, but however they come out, they must state that not only in good scientific terms but in terms that can be understood by judges, because ultimately it is the judges who will either enforce or not enforce those monographs.

Mr. FOUNTAIN. You do not ask for legal opinions but scientific opinions?

Mr. HUTT. I ask for scientific opinions.

Mr. FOUNTAIN. Regardless of the legal opinion?

Mr. HUTT. I ask for third grade English so they are understandable to everyone.

Dr. SCHMIDT. Including judges.

Mr. FOUNTAIN. We have so many things to attend to here we do not purport to be qualified to pass judgment. As I said, we are concerned with determining whether or not FDA has been acting expe-

ditiously and properly to resolve questions raised about the safety of new drugs.

More than 9 months have elapsed since Prof. Joseph Page urged the panel to consider reviewing zirconium aerosol antiperspirants on a priority basis, and more than 8 months since the panel decided that zirconyl aerosol in antiperspirants should be given priority attention.

Six months have elapsed since the panel voted unanimously that zirconium aerosols are not generally recognized among experts as safe, and almost 5 months since the panel gave the Commissioner of the FDA a statement detailing the basis for its decision that the zirconium aerosols should be placed in category II, the not recognized as safe category.

Three months have passed since the panel reiterated its earlier decision to place zirconium aerosols in category II.

Finally, 1 month has passed since the panel chairman informed the FDA Commissioner, on March 25, that the panel had once again voted to place zirconium aerosols in category II, this time recommending that they be taken out of interstate commerce. Your answer to that was that you wanted them to give you a full report with all of the evidence to back it up.

What is the position of FDA on whether or not zirconium sprays are generally recognized as safe among qualified experts?

Dr. SCHMIDT. During the past month since they gave me that handwritten note, the panel has been laying out the evidence and rationale. You heard that they are in session today or tomorrow.

Mr. HUTT. Tomorrow and Friday.

Dr. SCHMIDT. They will be finishing that report. Until I have that report I do not have a recommendation other than a very brief one from the panel.

They will state in that what they believe, and at that point, then, we will evolve our position.

Mr. FOUNTAIN. As of now you do not have a position?

Dr. SCHMIDT. No, sir. I have no recommendation from them. I do not have their evidence. I do not have their rationale.

Mr. FOUNTAIN. You have recommendations. What you are saying——

Dr. SCHMIDT. I have the sketchy one which stated that the chairman agreed is inadequate.

Mr. FOUNTAIN. They did give a report, as I recall.

Dr. SCHMIDT. No, sir. What they did in November is to come out with a report, the purpose of which was to gain comment. What I would point out to you is that the panel has not considered the hazard from zirconium sprays sufficiently immediate to recommend to me an alteration of the process until March 25.

Mr. FUQUA. I am not a chemist, but zirconium is in various antiperspirants. Are they all the same formula?

Dr. SCHMIDT. They can vary.

Mr. FUQUA. When you say zirconium it is not one specific formulation?

Dr. SCHMIDT. When I use the term zirconium, I include the element plus the various complexes.

Mr. FUQUA. I understand you to say there are different formulations?

Dr. SCHMIDT. Yes, sir.

Mr. FUQUA. Such as in soft drinks?

Dr. SCHMIDT. Talking about sodium, there is sodium chloride, sodium cyanide.

Mr. FUQUA. They are entirely different?

Mr. HUTT. Hopefully.

Mr. DRINAN. I followed the writing of Professor Page. In the New Republic there is another article. During the past 9 months, how have you handled representations from the industry about aerosols and related things? Suppose they inundate you with letters and briefs? Suppose they say they have changed the formula?

Do you people stay out and say it all has to go through the advisory committee?

Dr. SCHMIDT. Yes, sir. During the last 9 months our principal action has been to tell the panel our criteria for successful action on their part.

They have actually arranged for the presentations by industry and world experts to them so they can conduct their review. Any letters I have received have been placed in the hearing clerk's office and forwarded to the panel.

Mr. HUTT. There was one letter by one company which requested a meeting that both the Commissioner and I attended. The sum and substance of that meeting was that we told them we could tell them nothing about it until we received the report from the panel.

Mr. DRINAN. Have some companies tried to alter the chemical formula so they would not be under the ban, if such comes out, from the advisory committee?

Dr. SCHMIDT. Not to our knowledge. First of all, any complex they have which they have developed would not be simply exchanged with another zirconium or other complex. They are waiting for the panel's report, evidence, and everything else.

Mr. FOUNTAIN. We will have to recess in a moment.

If FDA decides to classify zirconyl aerosols in category II, as the panel recommended, how long would it take after you get additional information before the industry will be required to submit NDA's for those products if they want to continue marketing them?

Mr. HUTT. Again one must look at the process. If we were to do it using the whole process, that would take perhaps 2 or 3 years. If we are to expedite it, that could take a much shorter period of time. One would have to give industry an opportunity to comment. We would probably do it by rulemaking. This would mean publishing a notice in the Federal Register, time for comment, and then a final order requiring an NDA, if the recommendation comes forward and if we pursue it.

Mr. FOUNTAIN. In the meantime, will they be permitted to ship in interstate commerce?

Mr. HUTT. Yes, sir.

Mr. FOUNTAIN. Aside from public health considerations which are the responsibility of FDA, I think it is apparent that your decision would have substantial economic consequences for certain firms. There is Procter & Gamble in their products, Sure and Secret. I am informed Carter-Wallace, the producer of Arrid, is planning to spend millions of dollars beginning in April to promote an Arrid zirconium-containing aerosol antiperspirant. You are familiar with their plan, I imagine.

Mr. HUTT. Yes.

Mr. FOUNTAIN. Do you know whether Carter-Wallace is going through with that promotional plan at the moment?

Dr. SCHMIDT. We do not.

Mr. FOUNTAIN. Apparently Gillette Co. feels that it is now in a poor competitive position because of the withdrawal of its zirconium aerosol product, and it, too, wants to get back into the market, if FDA will allow Sure and Secret to be on the market for any length of time. Therefore, I think time and speed of FDA action is important as we look at this picture.

Dr. SCHMIDT. I would agree. We have told everyone who inquired that we would very rapidly go through this process.

Mr. FOUNTAIN. Thank you again. We will have to suspend.

The subcommittee will adjourn until Friday morning, May 9, at 9:30.

Can you make it then?

Dr. SCHMIDT. Yes, sir.

Mr. FOUNTAIN. The subcommittee stands adjourned.

[Whereupon, at 12:08 p.m., the subcommittee adjourned, to reconvene at 9:30 a.m., Friday, May 9, 1975.]

USE OF ADVISORY COMMITTEES BY THE FOOD AND DRUG ADMINISTRATION

(Part 2)

FRIDAY, MAY 9, 1975

HOUSE OF REPRESENTATIVES,
INTERGOVERNMENTAL RELATIONS
AND HUMAN RESOURCES SUBCOMMITTEE
OF THE COMMITTEE ON GOVERNMENT OPERATIONS,
Washington, D.C.

The subcommittee met, pursuant to notice, at 9:45 a.m., in room 2247, Rayburn House Office Building, Hon. L. H. Fountain (chairman of the subcommittee) presiding.

Present: Representatives L. H. Fountain, Don Fuqua, and Robert F. Drinan.

Also present: Delphis C. Goldberg, professional staff member; Gilbert S. Goldhammer, consultant; and Richard L. Thompson, minority professional staff, Committee on Government Operations.

Mr. FOUNTAIN. The subcommittee will come to order.

Let the record show that a quorum is present.

Before our hearings were recessed on April 23, I observed that whatever decision FDA makes on the zirconium aerosol antiperspirant, it will have substantial economic consequences for certain firms, particularly for Procter & Gamble, promoters for Sure and Secret sprays already on the market, and for Carter-Wallace, currently test marketing a similar aerosol product, and the Gillette Co., which now wants to reenter the zirconium aerosol antiperspirant market.

I was about to discuss the Gillette Co.'s motivation for returning to the marketplace when it became necessary for us to recess.

Earlier I had inquired as to whether or not Procter & Gamble had filed an NDA for zirconium aerosols or whether it was true, as Professor Page had alleged, that no NDA had been filed.

I do not know whether you, Dr. Schmidt, or you, Dr. Crout, but one of you had replied that an abbreviated new drug application had been submitted by Procter & Gamble for the aerosols in 1972.

Mr. Goldhammer informs me that on at least three or four occasions in the last 6 weeks he specifically asked FDA to tell us whether any applications had been filed or approved for any zirconium aerosols. The answer given each time was "No."

We now have what appear to be facts on that. We inquired of Procter & Gamble and were informed that some 16 years ago they filed a new drug application for zirconium-containing creams and roll-ons with FDA.

Are you familiar with this filing? I know this was before your day, Dr. Schmidt.

STATEMENT OF ALEXANDER M. SCHMIDT, M.D., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE; ACCOMPANIED BY J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS; PETER BARTON HUTT, CHIEF COUNSEL; ROBERT C. WETHERELL, JR., DIRECTOR, OFFICE OF LEGISLATIVE SERVICES; ROBERT G. PINCO, CHIEF, DIVISION OF OTC EVALUATION; MARK NOVITCH, M.D., DEPUTY ASSOCIATE COMMISSIONER FOR MEDICAL AFFAIRS; AND DAVID M. LINK, ACTING DIRECTOR, BUREAU OF MEDICAL DEVICES AND DIAGNOSTIC PRODUCTS

Mr. HUTT. Yes. That was for the nonaerosol product. We testified at the last hearing that such an NDA had been filed and approved.

Mr. FOUNTAIN. The NDA was approved?

Mr. HUTT. Yes, sir.

Mr. FOUNTAIN. We were also informed that Procter & Gamble submitted to FDA an abbreviated new drug application covering the aerosol zirconium sprays on January 10, 1972. This application, we have been informed, specifically named the product Secret but the application covered a formula range which also covered the Sure product.

Is the information we received from Procter & Gamble accurate?

Mr. HUTT. Yes, indeed it is.

Mr. FOUNTAIN. I am placing into the record a copy of an FDA letter dated June 20, 1972, provided to the subcommittee by Procter & Gamble, which discloses the disposition FDA made of the P. & G. abbreviated new drug application.

I shall read the letter in full:

Reference is made to your abbreviated new drug application dated January 10, 1972, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Secret (aluminum hydroxychloride, zirconyl hydroxychloride and hexachlorophene) antiperspirant.

Pursuant to the policy of review of over-the-counter drugs as stated in the Federal Register announcement of April 20, 1972, the material you have submitted will not be reviewed at this time but will be handled by the appropriate OTC panel at a later date.

The material you have submitted will be retained in our files.

This letter was signed by Dr. Paul A. Bryan, M.D., Director, Drug Efficacy Study Implementation Project Office, Bureau of Drugs.

[The letter referred to follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., June 20, 1972.

THE PROCTER & GAMBLE CO.,
Cincinnati, Ohio

GENTLEMEN: Reference is made to your abbreviated new drug application dated January 10, 1972, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Secret (Aluminum hydroxychloride, Zirconyl hydroxychloride and Hexachlorophene) Anti-perspirant.

Pursuant to the policy of review of over-the-counter drugs as stated in the *Federal Register* announcement of April 20, 1972, the material you have submitted will not be reviewed at this time but will be handled by the appropriate OTC panel at a later date.

The material you have submitted will be retained in our files.

Sincerely yours,

PAUL A. BRYAN, M.D.,
Director,
Drug Efficacy Study Implementation Project Office,
Bureau of Drugs.

Mr. FOUNTAIN. In its reply FDA expressed no guidance that I can see to the company as to whether FDA would oppose the marketing of the drug in the absence of an approved abbreviated NDA, or whether the drug is not a new drug within the meaning of the law.

What is your opinion one way or the other as to whether this should have been given P. & G.—that either it is a new drug requiring an approved NDA, or it is not a new drug and does not require a new drug application prior to marketing?

Mr. HUTT. At the time the letter was written, Mr. Chairman, that was clearly our policy. That letter was entirely correct. We were not opposing the marketing of that product as a new drug. It could go on the market, and it would, along with all other OTC drugs, be reviewed pursuant to the OTC drug review.

Mr. FOUNTAIN. Then the company was justified in marketing the product on the basis of your June 20, 1972, letter?

Mr. HUTT. The company certainly was justified in marketing it.

Dr. GOLDBERG. For clarification, Mr. Hutt, would it be correct to infer from your statement that FDA regarded this as a new drug——

Mr. HUTT. I apparently misspoke. The Commissioner pointed out to me I used an incorrect term. When I said new drug I meant newly marketed drug and not new drug in the statutory sense. Therefore, I misspoke.

If we had regarded it as a new drug at that time that letter would not have been sent and we would have opposed marketing.

Dr. GOLDBERG. Then you would classify it as a drug that is generally recognized as safe and effective?

Mr. HUTT. Yes; at that time.

Dr. GOLDBERG. Without examining the data the company had submitted in support of its application?

Mr. HUTT. That is right. What we were doing at that time was on the basis of taking the general knowledge of zirconium that had been, as we all know, marketed for some 16 years in deodorants and antiperspirants. We were not raising objections to the marketing of the product while the whole class of zirconium-containing antiperspirants was being reviewed by the OTC drug panel.

Dr. GOLDBERG. Had it been previously marketed in aerosol form?

Mr. HUTT. No; to my knowledge it had not.

Dr. GOLDBERG. Would that not have presented a new situation with respect to the possible hazard of inhaling zirconium?

Mr. HUTT. It could have, yes. However, once again we were in the process of an OTC drug review which was designed to ferret out those issues, and it was simply concluded that that was the proper way to go about it.

Mr. FOUNTAIN. Now, after the company has undoubtedly spent millions of dollars in promotion, and after millions of dollars of zir-

conium merchandise has been placed on the market, you are in the position of having to make a decision which you apparently did not make in 1972. If you decide that the product is a new drug requiring a new drug application, then all the merchandise now on the market, as indicated by your testimony of April 23, is illegal and subject to confiscation. In other words, it is contraband. Is that correct?

Mr. HUTT. If we decide it is a new drug, once we go through the entire administrative process, yes, sir. That would be correct.

Mr. FOUNTAIN. I believe that in the case of the drug efficacy review covered by your so-called DESI orders, products which had been evaluated by the NAS/NRC panels as ineffective or lacking evidence of efficacy, had their NDA's revoked. Such drugs were then in the status of being on the market without approved NDA's. I believe it is FDA's policy to require the recall of such products. Am I correct?

Mr. HUTT. Not in all instances. It depends upon the type of drug and a lot of other factors. In some instances we have required recalls and in some we have not.

Mr. FOUNTAIN. In this connection we placed into our April 30, 1974, hearing record, an April 19, 1974, memorandum to you, Dr. Crout, from L. M. Baukin, Director of FDA's Division of Regulatory Operations in the Bureau of Drugs, and this letter now appears at page 447 of the hearing record on the use of advisory committees by the Food and Drug Administration. Mr. Baukin's letter states in part:

> Under established DESI compliance procedures, outstanding stocks of a drug named in a final order withdrawing approval of an NDA are subject to removal from trade channels by recall to the retail level.

Has Mr. Baukin expressed FDA policy correctly?

Mr. HUTT. I checked into that on several occasions in the course of the last 2 years. I find that is not an absolutely rigid uniform policy, Mr. Chairman. It expresses a very general policy probably in which the majority of instances it is followed, but it is not a uniform and absolute policy. I do not believe Mr. Baukin intended to express it as such. He said it is subject to this policy, but that does not mean there are not exceptions.

Mr. FOUNTAIN. At this point I will turn to where we left off on April 23, when I mentioned the Gillette Co's. interest in resuming the marketing of an aerosol zirconium antiperspirant.

I am placing in the hearing record a Gillette Co. letter of March 24, 1975, to the chairman of the antiperspirant review panel referring to the panel's November 1974, and January 1975, classifications of the zirconyl aerosols in category II while at the same time advising the Commissioner that marketing of such products may continue during toxicological testing by the industry. The letter states in part, and I quote:

> After voluntarily recalling two antiperspirant products containing zirconium, Gillette reformulated a new zirconium antiperspirant which was cleared for national marketing in the spring of 1974. Marketing was delayed, however, when the Panel expressed concern about the safety of ZCAA's and decided to consider ZCAA's out of turn in the Panel proceedings. We have continued to delay marketing the zirconium product believing that the safety issues would be resolved by the Panel and the FDA. However, the action taken by the Panel, instead of clarifying the matter, has further confused it.

Gillette then asked six questions, most of which relate to the panel's classification of zirconyl aerosols in category II and the effect of that classification on the continued marketing of such products by members of the industry, including Gillette. Question 4 is pertinent to our inquiry today, and it reads in part as follows:

We understand that we can expect the Panel to submit its proposed monograph to the Commissioner about the end of 1975, and the publication of a final monograph will be in 1977 after compliance with the other administrative steps. Compliance with testing requirements could delay administrative action against ZCAA's which have not demonstrated adequate safety until 1978 or 1979. Is our understanding of the timing correct?

Page 3 of the letter states in part, and I quote:

As the Panel can appreciate, it would appear at present that no action will be taken on ZCAA's until 1978 or 1979 . . .

It seems to us incongruous in the extreme that a product can be found not to be GRAS and still be permitted on the market for many years before the questions of safety are finally resolved, and yet this appears to be the context in which Gillette must make its decision on zirconium.

I might add that GRAS means "generally recognized as safe." [The letter referred to follows:]

THE GILLETTE CO.,
Boston, Mass., March 24, 1975.

Dr. E. WILLIAM ROSENBERG,
Chairman, Antiperspirant OTC Drug Review Panel,
The Food and Drug Administration,
Rockville, Md.

[PRIVILEGED AND CONFIDENTIAL]

DEAR DR. ROSENBERG AND PANEL MEMBERS:

The Antiperspirant OTC Drug Review Panel has spent considerable time reviewing zirconium-containing aerosol antiperspirants (ZCAA). These products were reviewed out of turn because the Panel was concerned about the potential toxicity of ZCAA's.

In November, 1974, the Panel unanimously classified ZCAA's in Category II, and although a recall of ZCAA's was not recommended, the Panel felt it was inappropriate for these products to continue in interstate commerce during the time that appropriate studies, to confirm or deny the safety of such products, were being conducted. Early in 1975, however, the Panel, while not changing its classification of ZCAA's from Category II, stated that the continued marketing of these products could be permitted contingent upon the vigorous pursuit of toxicological testing by industry.

After voluntarily recalling two antiperspirant products containing zirconium, Gillette reformulated a new zirconium antiperspirant which was cleared for national marketing in the spring of 1974. Marketing was delayed, however, when the Panel expressed concern about the safety of ZCAA's and decided to consider ZCAA's out of turn in the Panel proceedings. We have continued to delay marketing the zirconium product believing that the safety issues would be resolved by the Panel and the FDA. However, the action taken by the Panel, instead of clarifying the matter, has further confused it. We are writing this letter to seek clarification of the Panel's position on ZCAA's before we make a final decision with respect to the marketing of a zirconium product. We would greatly appreciate receiving the Panel's answers to the following questions:

1. Do we correctly understand that, as far as the Panel is concerned, Gillette and any other company are free to market products containing zirconium and to do so responsibly since any questions of health and safety are so remote there is no health hazard involved?

2. Does the classification of ZCAA in Category II mean that the Panel has found these products not generally recognized as safe (GRAS)?

3. Was the Panel's statement that the major risks associated with these products are primarily long-term based upon the continued marketing by only one manufacturer or did the Panel take into consideration the national marketing of ZCAA's by other industry members? Would marketing by Gillette and others change the Panel's views?

4. We understand that we can expect the Panel to submit its proposed monograph to the Commissioner about the end of 1975, and the publication of a final monograph will be in 1977 after compliance with the other administrative steps. Compliance with testing requirements could delay administrative action against ZCAA's which have not demonstrated adequate safety until 1978 or 1979. Is our understanding of the timing correct? Is the Panel aware of any developments which would accelerate the timetable?

5. Does the panel plan to require any labeling for ZCAA's (cautions, safety statements, etc.) different from other antiperspirants prior to issuance of the monograph?

6. Is the Panel aware of any tests which can be quickly run to furnish preliminary safety information?

As the Panel can appreciate, it would appear at present that no action will be taken on ZCAA's until 1978 or 1979. If Gillette's competitors utilize the delay built into the monograph approach to go to market with other ZCAA's, Gillette will have to review the decision it made to delay marketing and decide how it can best meet its responsibilities to the consumer and still protect its market position.

It seems to us incongruous in the extreme that a product can be found not to be GRAS and still be permitted on the market for many years before the questions of safety are finally resolved, and yet this appears to be the context in which Gillette must make its decision on zirconium.

In view of the importance of this issue and the time elapsed we would greatly appreciate an immediate response to this letter from the Panel.

Very truly yours,

ROBERT W. VAN CAMP,
Group Vice President.

Mr. FOUNTAIN. This letter apparently was timed to coincide with the panel's March 24 and 25, 1975, meeting, for it appears to have been considered by the panel during its closed meeting on March 24, 1975. I am placing into the record pages 2–71 to 2–93 of the verbatim transcript of the proceedings of that closed meeting. The names of panel members who participated in the discussion have been deleted, but FDA employees are identified.

[The material follows:]

THE FOOD AND DRUG ADMINISTRATION, CLOSED SESSION—ANTIPERSPIRANT PANEL

(March 24, 1975)

SPEAKERS

E. William Rosenberg, M.D., Chairman, Division of Dermatology, University of Tennessee.
J. Wesley Clayton, Ph.D., Director, Toxicology Program, The University of Arizona.
Charles A. Evans, M.D., Ph.D., Department of Microbiology, SC–15, University of Washington.
Zenona Wanda Mally, M.D., 1835 Eye St., N.W., Washington, D.C.
Jane M. Rosenzweig, M.D., 1970 Jackson St., San Francisco, California.
Robert J. Scheuplein, Ph.D., Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts.
Eli Shefter, Ph.D., Department of Pharmaceutics, State University of New York, Buffalo, New York.
March Bruch, Food and Drug Administration, Executive Secretary, Rockville, Maryland.
Marsha Gardner, Consumer Federation of America, Garrett Park, Maryland.
Robert Giovacchini, Ph.D., The Cosmetic, Toiletry and Fragrance Association, Inc., Gillette Medical Evaluation Laboratories, Rockville, Maryland.
Lee Geismar, Food and Drug Administration, Panel Administrator, OTC Staff, Rockville, Maryland.
Bob Pineo.
Peter Hutt, Lawyer.
George Thompson.

Dr. ———. The record will show Mr. Hutt.

Mr. HUTT. I have a small time problem. I can stand until five minutes to four and then I will have to come back.

I have got to take care of a problem at exactly four o'clock with the Commissioner.

I just read the Gillette letter. And understood that you wanted to discuss it.

And I think it raises a question that requires us to go back and say how did we ever start along this road that we are going on the over-the-counter drug review.

Because this issue arises for roughly 400,000 products. Not this product.

It rises. Every panel has the same issue with regard to one or more products.

Now, we just released two days ago the laxative report. And there are products in the laxative report which flatly are found by the panel not to be generally recognized as safe.

And so you can ask the question, each one of you and each one on that panel can ask the question, "Well, why weren't those taken off the market five years ago? Or two years ago. Or whenever?"

And the answer is to go back and see where we were in late 1971, when we set up this exercise. To understand why we have to follow through in a routine, orderly, systematic way.

And in addition as I pointed out to you every time we've met, why we have specialized procedures where they are needed for real sort of danger to health type problems, things that should be done immediately.

Now, let me go back and trace a little bit of that background and history.

What we, when I came in September of 1971, where we were was exactly as follows.

We had eight law suits going in the courts, against either important or minor over-the-counter drugs.

We had a case against Aspersleep; I don't know how many of you have ever heard of that famous drug.

We had a case against Zerac acne gel; another real big winner.

We had a case against Vice-Spice, which was a fake aphrodisiac.

We had a case against two hang-over remedies. Quick Over, and I forget the names of them.

The only important one that anybody had ever heard of was Excedrin P.M. A case against Excedrin P.M. And some equally crazy products.

Now, I figured that my staff of 18 lawyers could handle that type of litigation on maybe 15 products a year.

And the facts of the market place were such that there were roughly 100,000 to 500,000 products out there. And I did a little bit of rough calculation, and divided 15 into somewhere between 100,000 and 500,000—it didn't really make much difference. Because the answer was that you never really got to the end of it.

On top of that, we litigated one of those cases, Zerac Acne Gel. I have never even heard of the product. Have you ever seen that?

Dr. ———. Yes.

Mr. HUTT. Have you really? Well, I don't know. We litigated that case all the way up through the U.S. Court of Appeals.

We had affidavits filed in the District Court. And they found that it was not generally recognized as being safe or effective

We went to the Court of Appeals. And the Court of Appeals—well, when the case was pending in the Court of Appeals, the attorney on the other side called me up one day. And said, "I would just like you to know that we changed our formula."

Now, what that meant was, we started all over again. Because just because we have the old formulation taken off the market, they could put a new formulation out, and we would start all over.

So I said that's that. To hell with it. I am not going to go through any more litigation.

I stopped all the litigation. All of it. Traded out all those cases. And we started along the rule making approach.

Because until we got the solid administrative rule making base to cover all OTC drug products, we were in the state of chaos, and could never, no matter how many years went by, could never handle the products.

Now, right off the bat, we knew there had to be exceptions.

And it was a real easy thing that taught us that lesson. The thing that taught us that lesson was hexachlorophine.

Because in January of 1972, well, we first unveiled the proposal in January, right at that time we were up to our ears in the hexachlorophine problem.

And we had to take immediate action on hexachlorophine, even before we gave it to the panel. We issued the notice of proposed rule making on hexachlorophine the day that we got the panel to even begin looking at the issue. It was literally the same day.

The same day of the Federal Register. We couldn't wait.

From the beginning, I told the Bureau of Drugs that there were basically two situations where we would take drugs out of turn.

One was where there was a danger to health. And the other was where there was just rampant fraud. Just fake cancer quacks and all that kind of stuff.

And we have held to that. In either of those two situations, we will not wait for the orderly administrative process. We realize that we've got to act immediately. And that's always the way FDA has gone about it.

But you can't let the exceptions overtake your rule. Or you would be back where I was in September 1971.

The fact that the laxative panel has come up with half of the products being unsafe or uneffective doesn't remotely surprise me. I expect that will be true as we go through everything over a period of time.

That doesn't mean that today, I should go out with that proposed regulation and take all those half of the products off the market.

To do that would put me right back where I can't afford to be.

Namely, putting all my resources into litigation rather than into covering all hundred or five hundred thousand products at once.

This is what I would call attention, that will exist as long as we adopt the rule making approach.

And it is the classic situation in cost benefit analysis, you give up something in the short term in order to get something in the longer term.

And if you don't give it up in the short term, you will never get to the long term results.

Now, let me go back to the exceptions because they are important.

Starting with hexachlorphine, which was the first exception, we said if there is a sufficiently great hazard which I as a lawyer am not about to define. Whatever that means. We will take that out of turn, and we will handle it even before it goes to the panel.

Then we got into TBS and we said if there is not a sufficiently great hazard, just take it away from the panel completely.

But the panel believes it is something we ought to take out of turn, once the the panel's report has been made, as we did with TBS, then we will also do that.

That is sort of an intermediate step. And if it is a lack of safety, but does not create a big enough health hazard to justify one of the other two approaches, then we will handle it in the ordinary course of business.

Now, those are the three options that we've got.

I think that Gary and Bob and I have tried to spell those out to you over a period of time. And maybe it is useful to go back and talk about those three options.

Then again, I wanted to lay out the historical background so you understood how we were coming at this.

And why certain things have happened. Let me continue for one moment, and then come back to those three options.

The people out in the industry aren't stupid. They see what we have done.

And they see in some instances where they can take advantage of it.

There is a new toothpaste called AIM. You have seen television advertisements.

Until the OTC review, we had required an NDA for every fluoride toothpaste.

Having adopted the policy of not litigating except in health or fraud issues, pending the OTC review, that particular company, and I don't remember which one it is, decided this was a good time to put out their new toothpaste without getting an NDA.

Their competitors came in complaining. And said, "Damn it. We had to get an NDA. How come they don't have to get an NDA?"

And we said it is really a matter of priorities and resources in FDA.

If I were to start litigating against every AIM type product, then I would have my 18 lawyers spread all over the courts of the country again on a piece meal *ad hoc* case by case basis instead of handling it on a comprehensive basis in this room.

And in the other panels like this. So it creates dislocations on a short term basis. There is no question about that.

There have been probably 20 or 30 products of that type that I can think of off the top of my head put on the market in the last year or two, taking advantage of that situation. And there, it puts me in a tough spot because I was the one who

sort of made the principle decision two and a half or three years ago that this was the intelligent way to go.

Because I would know that in five years from then, maybe two years from now, we will have the full OTC business under control as opposed to 45 products under control.

And I was willing to give up what I had to give up in order to gain that.

Now, let's come back though to this issue of the Gillette letter.

The Gillette letter poses the issue to you that really we have been posing for the last few months.

It is phrased a little differently, but it is the same damn issue.

The issue is whether either you have sort of a huge safety problem that justifies the hexachlorophine approach.

Or an intermediate safety problem that justifies the TBS approach.

Or simply the usual safety issues, maybe a little bit greater. But roughly in the same category as the antacid approach found.

Dr. ———. Tell me again about that TBS approach.

Mr. HUTT. OK. The TBS approach was to go through the report stage. And at the end of the report to say instead of following and having a tentative order and then a hearing on the tentative order, then a final order, which takes time.

And as of that time, you have a separate notice of proposed rule making. On which there is time for comment and then a final order.

Which would be changed so you would shorten the time period involved roughly in half, I would say as a rough estimate. You would cut the time period in half.

And if anything came out ultimately in the whole procedure, then you could always go back and modify the regulations dealing with TBS.

And that is still, that is an option that is still available. Any of these three options are available here.

But what I wanted to do, and I still have some time. But I wanted to lay it out in perspective to see the whole scene. Because you can't just take this one product and make any sense out of anything.

You've got to put it into the entire spectrum of what the agency is trying to do

And if it deserves special treatment under either hexachlorophine or the TBS approach, then you ought to make that recommendation.

And you ought to spell out the reasons which were spelled out at the time of hexachlorophine and TBS.

Now, I think about you and Gary sitting there, and Mary, if you want to add—if you think that I have left anything out.

Ms. BRUCH. Well, I think the one thing on TBS is one of the issues that the panel debated was that the hazard was there and they saw no way that it was going to go away.

The testing to prove that you could alter it was probably impossible and unethical.

And that they felt that was one reason—that they asked TBS.

Mr. HUTT. In both hexachlorophine and TBS, we had demonstrated human harm.

Without any questions. With the hexachlorophine, we had dead babies in France.

In TBS, we have extraordinarily well documented cases of sensitivity, photo sensitivity, all over the country, and indeed, all over the world.

The only issue was whether it was being reduced because of getting an impurity out or not. That is still an issue as far as I am concerned.

We haven't resolved anything. We haven't put out a final order.

That in my opinion is not an absolute requirement in the sense that if this panel just felt very strongly that although there is no definitive proof of harm, there is such a likelihood or probability or the harm is so severe that no reasonable man should put up with it in the intervening period of time, then you can make the same recommendation.

I am not saying that you have to wait for dead bodies. And clearly that has never been the FDA's approach to things, and we would not approach it here.

But you have to have—the one thing is, you know, I have demanded of you, and I demand of any scientist or of any lawyer, you have got to have reasons that will convince people and you have got to spell them out in words of one syllable and third grade English.

Because the lawyers who will look at it, and sometimes you need third grade English for all of us to understand.

And it has to be articulated in a way that anybody would read it and say, "Yes. I see the problem. And that makes sense."

That's all I demand. Bob, you wanted to—?

Mr. PINCO. I think, I wasn't here at the very beginning. I think, what I understand seems to be troubling the panel is that having categorized the thing into these, the ingredients as it were, into category two, they would like to see the thing happen immediately.

And I think we had discussed the limits. In fact, I mentioned it at the open session and we were talking later, a few of us, about the limits that we have in terms of where the agency is able to go and on what basis.

And it still places, again in this particular situation, I think that they are troubled by the fact that everyone is going to run to the market place.

And you know, there will be five or six brands or so on in the market place.

After they have already in sense made their comparative decision, this is where they want it to go.

Mr. HUTT. We have that problem again in all seventeen panels.

And we have to—the one thing that I also insist upon is absolute uniformity of treatment.

If we are going to say that a given product can stay on the market, we cannot then say that no one can come out and compete with them.

On the other hand, if we are going to—either everyone goes on or everybody comes off.

It has got to be that way. Unless you as a panel can say there is a distinguishing factor that this particular product has been proved safe.

In which case, you can say everybody ought to do the same test. And also prove theirs safe.

And I am obviously not going to get into your specific zirconium problem, because I don't know a damn thing about it.

I wouldn't know what should be done to prove safety. Or I wouldn't know a safety test, I imagine, if I saw it.

So all I can do is to deal in generalities. ———, I wonder if it would be possible for you, either off the record, or you could perhaps choose not to, stop speaking as an industry liaison and tell us a little bit about what went on at the Gillette company, if you know about it.

Or would you rather not do that?

Dr. ———. I think he should not be put in a position of doing it if I can speak for him.

I think—the agency has had a general rule that the industry liaison in discussing particular company things ought to do it in an open session.

Mr. HUTT. OK.

Dr. ———. I don't think we should put ——— on the spot.

Dr. ———. I think he spelled it out rather clearly.

I think that I see a place for this to go in those three categories that you described.

It is just a little dismaying to us to feel, as I feel, that as a result of our putting it into a category 2, primarily because of our concern for its hazard, we have actually encouraged its distribution in the market place.

Mr. HUTT. Well, I would not agree quite with your characterization because, putting it in category 3 or 2—I mean, putting it in 2 as opposed to 3, didn't encourage it going into the market place.

Dr. ———. Well, the time delay between the implementation of the final report and the final monograph——

Mr. HUTT. Well, I understand that. Which is why we have the exceptions. Without a question.

The difficulty is when you start down a process of this kind, and that the law does have a concept that all of you have heard of called due process of law.

The fact that this panel makes a recommendation doesn't mean it is automatically accepted.

You know, there are rights to appeal up to the Commissioner. There are rights to appeal to the Court.

And that is part of our legal process. So all that we could do would be to expedite the process.

But they would still be entitled to their legal procedures.

And putting it in two I don't think has encouraged anyone to do anything.

I think it has encouraged them to test. And if indeed there is not enough testing being undertaken, then I think that the Commissioner, and I know I can speak for him on this without asking him, the Commissioner would be willing to do anything that you recommend to make sure that that testing is undertaken. And that the people get the message if they haven't gotten it.

I certainly would be willing to do that.

Dr. ———. Well, that confusion is certainly evident in that letter that we received.

Mr. HUTT. Well, I think that the greater confusion in that letter if I can speak with my friend Dr. ——— present, is a lack of real understanding of the OTC review. And ———, that is not meant personally.

In all seriousness, the delay that you talk about is inherent in the legal process. And it is inherent in the way that we have gone about this particular project. Which is why we built into the process the exceptions that I talked about.

But I think you can appreciate that it would be very difficult for me now, on the laxative report released two days ago and rush out into the courts. And start bringing law suits against all the products, where, first of all, they haven't completed their legal process.

And second, overnight, I would have used up all the legal resources of the agency bringing those lawsuits.

I would be jumping into a race without finishing the process. And where there is justification, we will do that.

Where there isn't, we have just simply said that we won't.

So that part of the letter that says it is incongruous for something to be in category 2 and still on the market, that's the way you answer that.

All of the things in the laxative report released two days ago that are in category 2 still have a right to submit comments.

At the end of the comment period, they have a right to request an oral hearing

And when the Commissioner rules against them, if he does, they have a right to appeal that to the Court.

We do not have arbitrary authority, nor I might add, have I ever suggested that we ought to have it.

That I don't think would be the answer either. I don't think any of you would want it.

That's not the way the Government does business. Although we are accused of it from time to time.

Mr. PINCO. ———, in the context of the information that was sent then to the Commissioner, what your thoughts were, I think it maybe becomes clear to the panel why there was no reaction.

I got that from Lee that you were sort of expecting action from the Commissioner.

But based upon the way we set it up, unless we were going to go this serious hazard route, which we all went around and determining getting that paper ready and so on, the only mechanisms that we saw of this point, and as Peter discussed, were the ones where your report comes out like the tribunsalane, in the regular mechanism.

So we didn't see the need to respond. I hope you didn't think that we didn't care. Because the Commissioner didn't——

Mr. HUTT. The Commissioner is quite well aware of this problem. To say the least.

Mr. PINCO. It is just that we didn't see another mechanism before.

Ms. BRUCH. Our serious problem really is in hexachlorophine, it was fairly easy because of an accident in the safety of the babies.

We probably have the actual cases in here where we were faced with the issues. We so far do not have proven clinical cases.

Mr. HUTT. There is one thing that I think could certainly be done at a minimum. And that is to make clear to everyone in the outside world what this panel and FDA expect in terms of testing. Beginning right now as opposed to beginning in four months, much less two years.

And if that has not successfully been done, that could be done. And I am sure very effectively.

And I think, for example, the panel could easily say right now on an issue of a sort of interim conclusion to be directed to the industries, here is the kind of testing that we would expect anyone would be doing today.

And if people are not starting that today, then when it comes time for your report, you might well recommend the TBS approach of speeding up the process.

You don't have to reach that decision today, because, obviously, you don't have your report in final draft form at this time.

Now, all I wanted to do right at this moment, the reason that I came down immediately when I read this letter and heard that you were going to talk about it, was to lay out some of those things.

I would be delighted to come back down either later tonight or tomorrow morning or whatever. Or I could give you a time.

Dr. ———. Just before you go, you spelled out for us very nicely the legal aspects. And of course, this is a country of laws. And we will abide by the law.

But you are a lawyer, and we are not. Let us now, the way you are prepared to tell us you don't understand or you don't know the scientific aspects. But you do know the law.

Let me speak for those of us who do not know the law. We seem to feel we realize full well where we are.

Let me set that out in words that are very clear. We have a situation which people who want to be dry under their arms can be as dry technically as possible, even with these sprays. By using an aluminum roll on.

People who chose to use a spray because they perceive a pleasure of a spraying rather than a rolling on, can be dry to the best one, come quite close to what these achieve.

So in terms of the benefits, we see very little benefit from this particular class of products. That is point one.

Very little additional benefit from these over either the roll ons, the zirconium creams, the Secret cream, the roll on, the aluminum sprays. Very little benefit.

Secondly, we perceive here the potential hazards which if it occurred would be of very large magnitude. Pulmonary fibrosis, which is a dreadful thing to happen to people.

And it could be happening on a very large scale with a little bad luck.

Only a few people worked in fluorescent tube factories. But lots and lots of people are breathing this thing.

If this thing causes trouble, it will cause a lot of trouble potentially.

And if it is a particularly nasty kind of trouble, where irreversible change occurs in the lung, that is the second one.

Third, the nature of this kind of disease, it comes on insidiously. It comes on slowly. It is hard to test for.

The natural history of these diseases is that it is a long time before doctors finally got on to them.

And people are very disappointed that it happened.

We find, as I indicated in my letter, no mechanism for coming to grips with early disease. Within the FDA as far as I can determine.

Industry has flat out done all it can to get these files closed, one at a time. They have not gone in there and followed through with a guy who says, "I have been using sprays all my life. This one makes me cough. What did you put in it."

They have not gone and tried to test this guy with fiberoctic bronchostomy and all kinds of things that could have been done.

They tried their best to quiet it down. In fact, statements of physicians determine nothing need to be done.

We can't go, "Which Position?" Their position or man's position.

It is very disturbing. This is another medical fact.

So if early disease be present, we are not in a position. We don't have the technology for knowing.

We have the theoretical question. If you have a question, you just ask it. You don't have the technology for knowing it.

Dr. ———. We have the technology, but it is not being applied.

Mr. HUTT. All right. Now, this gets right back, if I could just drop a footnote, and come back to it, to what I said earlier.

Here things are not being done. That should be done.

That is something——

Dr. ———. That is one of the things that——

Mr. HUTT. We can deal very directly with that, and very quickly, and very effectively.

Dr. ———. OK. That's one of the things that we can state. That we haven't touched on that—we haven't.

The next thing is we have now one company selling, claiming a market advantage. There time is up.

We are now going to have Carter-Wallace, we are now going to have Gillette. We can expect that if we don't have anything in two years, this stuff is going to sweep the market. And everybody is going to be using this stuff all the time. The issue is going to be magnified.

Mr. HUTT. OK. Let me summarize by saying that the way this is set up, I would be violating the FDA rules if I were to give you advice.

It is your job, so with Mary, so with Bob. If I were to say you are to do "X," or you ought to do any of the alternatives, I would then probably get a law suit, either by the consumer group that would be disappointed or by the industry who would be disappointed. One or the other is going to be disappointed.

Now, I will steadfastly refuse to get FDA into that. And so with all the rest of that.

Because that will foul up the whole system, and we will have to start out with scratch.

I can lay out the alternatives. You can lay out your concerns and what you can prove and can't prove.

And what you've got to do is make a recommendation now to the Food and Drug Administration as to what you think the best approach is.

At that point, then FDA comes in and we can get into it and say, "Yes, we agree." "No, we don't agree." Whatever.

Recognizing that I don't know what the outcome will be of your deliberation or of our deliberations.

But for us to now tell you what we want you to do is to recommend to us this, that, or the other thing would be wrong.

That would just foul up the whole system. And I think you understand that. I will be happy to come back if you like . . .

Mr. FOUNTAIN. These pages disclose that shortly before 4 p.m. on March 24, 1975, Mr. Hutt appeared before the panel and said: "I just read the Gillette letter and understand that you wanted to discuss it."

Mr. Hutt, your discussion with the panel provides good insight into the origins of the monograph, or drug class, approach in the regulation of OTC drugs, the procedures adopted by FDA, and the problems and possible deficiencies which have arisen.

In that discussion you indicated that you stopped all litigation involving OTC drugs because you felt it was futile to proceed on a case-by-case basis. Can you fix the date when you stopped all litigation involving OTC drugs?

Mr. HUTT. There was no particular date. It would have been in the course of 1972 after we had decided to go ahead with the broad rulemaking approach. I had learned, as I related at the last hearing, Mr. Chairman, that the litigation was proving to be even more futile than I had originally thought. At least one company had totally reformulated its product and I was faced with going back and starting the litigation all over again, even on just that one product.

However, there would have been different dates for different pieces of the litigation.

Mr. FOUNTAIN. During the course of the litigation about one product, the company had reformulated the product?

Mr. HUTT. Indeed, when that case reached the U.S. court of appeals. That was the *Xerac Acne Gel* case.

Mr. FOUNTAIN. Was this about the time you published the proposed 1972 monograph regulation?

Mr. HUTT. It is my recollection it was after that time. Again, it spanned at least 6 months.

Mr. FOUNTAIN. You told the panel that when you assumed your present position as FDA General Counsel in September 1971, the agency had eight lawsuits in the courts against OTC drugs.

Mr. HUTT. That was a rough number; yes.

Mr. FOUNTAIN. Approximately?

Mr. HUTT. Yes.

Mr. FOUNTAIN. One case was litigated. In that connection you said:

We litigated one of those cases, Xerac Acne Gel. I have never even heard of the product. * * * We litigated that case all the way up through the U.S. court of appeals. We had affidavits filed in the district court. And they found that it was not generally recognized as being safe or effective.

I assume from that statement that you won that case in the U.S. district court?

Mr. HUTT. We won that case in the district court. That is the one that proved to be so futile because, when we got to the U.S. court of appeals, the company informed me they had reformulated the product which would have made the appeal in the U.S. court of appeals moot.

If I recall correctly, Mr. Chairman, and I would have to go back to the record and check, in that case we concluded not to waste our time with the appeal in the U.S. court of appeals. Instead we reached an agreement with the company that they would abide by whatever came out of the rulemaking; the final monograph for that class of drugs. The litigation was therefore dropped. That is my recollection.

Mr. FOUNTAIN. We shall try to put this into context by putting into the record the statements which you made at the time.

Mr. HUTT. Surely. My recollection is that it is virtually the same thing I said, indeed, at the last hearing.

Mr. FOUNTAIN. The firm apparently appealed the decision to the court of appeals since you state, and again I quote:

> We went to the court of appeals. And the court of appeals—well, when the case was pending in the court of appeals, the attorney on the other side called me up one day and said "I would just like you to know that we changed our formula."

You then told the panel, and once again I quote:

> Now, what that meant was, we started all over again. Because just because we have the old formulation taken off the market, they could put a new formulation out, and we would start all over. So I said that's that. To hell with it. I am not going through any more litigation. I stopped all the litigation. All of it. Traded out all those cases. And we started along the rulemaking approach.

How were those cases traded out?

Mr. HUTT. By exactly what I just described, as I recalled, in the *Xerac Acne Gel* case. We got a stipulation from the company that they would comply with the final monograph coming out of the OTC drug review.

Mr. FOUNTAIN. Were you referring to the eight suits already in process?

Mr. HUTT. Yes. I would have to go back on each of those eight. There was one I disqualified myself and my staff handled that. I think they got a change in the formulation on that drug.

My recollection is that Excedrin PM was never terminated. That is still pending in the court because the attorneys on the other side would not agree to a stipulation.

My recollection is that we did proceed through summary judgment in one of the cases, Vice Spice, that famous aphrodisiac I mentioned last time which is made of paprika, and that the remainder we succeeded in stipulating, and thus as I put it colloquially to the OTC drug panel, traded them out.

Mr. FOUNTAIN. How many of them involved charges that OTC drugs were new drugs not covered by approved NDA's?

Mr. HUTT. All of them. That was the whole purpose—to get rid of all that useless litigation which had really not achieved anything except waste the time of my staff and the Bureau of Drugs.

Mr. FOUNTAIN. Being an attorney I can understand some of your feelings in a matter of this kind. However, am I justified in assuming from the reading of your statement to the panel that you were simply throwing in the sponge, so to speak, in a moment of frustration over what had happened? I get the impression you decided at that point, and I think perhaps you have said that, that it was futile to try to cor-

rect OTC drug violations as they were encountered because FDA hadn't accomplished anything meaningful in bringing the actions it had. Is that a justifiable inference?

Mr. HUTT. It was futile to adopt an outmoded means of enforcement, that is, the case-by-case litigation approach.

I think, Mr. Chairman, at this time, if you would permit it, I would like to read from some of the court decisions which have subsequently been handed down reflecting the courts' conclusion that what I did at that time made eminently good sense.

There are several court decisions in which the issue of the legality, the propriety, and the good sense of the OTC drug review has been raised.

I have a list of five of them here ranging from district court decisions to the U.S. Supreme Court.

Mr. FOUNTAIN. You can insert those in the record. You can summarize them if you wish.

[The documents referred to appear in the appendix at pp. 318–331.]

Mr. HUTT. In Judge Bryant's decision of October 1972 in the *American Public Health Association* case, he exempted all over-the-counter drugs from his order for implementing the DESI review on the ground that use of the over-the-counter drug review procedures were eminently more sensible and reasonable.

Mr. FOUNTAIN. This was efficacy only, and not safety?

Mr. HUTT. Efficacy only, but since the OTC review procedures involve safety, it involved safety as well.

Mr. FOUNTAIN. Each company had a new drug application on file with FDA?

Mr. HUTT. No, not the "me too" drugs, none of them, of which there are 13.

In a case that was litigated down in Georgia, the *Colintrol 80* case, the issue arose as to whether this was the kind of thing FDA should be doing. The court quoted from earlier court of appeals decisions saying that "agencies must exert the greatest resourceful, imaginative ingenuity in devising procedures which in a day of ever-expanding dockets will permit the regulatory process to function properly with reasonable dispatch."

Then, after that quotation, they said this about the OTC review:

"It would appear to the court that in the instant case the FDA has attempted to fashion procedures calculated to achieve precisely the result applauded by the fifth circuit court of appeals" in the quotation I just read.

The precise issue of the legality of the over-the-counter drug review arose in a case on the west coast. Here is what the district court judge said in the *Smart* case:

> It has been thought, possibly mistakenly, that over-the-counter drug remedies are so safe and effective, and Congress is now, as I understand it, inquiring into whether those expectations on OTC drugs have been appropriate. I take it to be fully within FDA's jurisdiction to make that determination and to establish a procedure for doing so as they have done here.

Then the court says:

> Advisory committees are policy-determining groups whose deliberations are entitled to protection.
>
> It seems to me here we have a very sensible, a very valid, a highly appropriate method of exploring a wide range of things that, if they were to be taken on an item-by-item basis, would be impossible ever to handle, and it is only by the kind

of approach that has been worked out here that the Congressional purpose can be achieved. It is obviously a proper purpose. It is in my view not only permitted but a highly desirable method of seeking to achieve the purpose.

More recently, and I would conclude with this, the U.S. Supreme Court, in the *Bentex* case, first lays out in detail the OTC drug review, and then goes on to discuss not only the propriety but the need to handle issues of this kind on a broad rulemaking basis that affects everyone at once.

The Court said:

> We think it is implicit in the statutory scheme, not spelled out in haec verba that FDA has jurisdiction to decide with administrative finality, subject to the types of judicial review provided, the "new drug" status of individual drugs or classes of drugs. The deluge of litigation that would follow if "me too" drugs and OTC drugs had to receive de novo hearings in the courts would inure to the interest of manufacturers and merchants in drugs, but not to the interest of the public that Congress was anxious to protect by the 1962 amendments, as well as OTC drugs and drugs covered by the 1972 act.

The Court goes on to say:

> A case-by-case approach is inherently unfair because it requires compliance by one manufacturer while his competitors marketing similar drugs remain free to violate the act.

They cite a good number of other cases in which the Supreme Court has urged Government agencies not to use the case-by-case litigation approach, which I discarded in 1972, but instead to go to a broad rulemaking approach which the Supreme Court endorsed in 1973.

Mr. GOLDHAMMER. I would like to attempt to put things into perspective.

First, going back to the *Bryant* case, that concerned the DESI review. Was not that DESI review a review of drugs for which new drug applications had been submitted but which had been cleared only on safety, and were now to be decided on the evidence of efficacy? The Food and Drug Administration then contracted with the National Academy of Science to review the data on efficacy for those drugs, which, as I say, were covered by NDA's?

Mr. HUTT. Yes, that is entirely true. That included, as you know, Mr. Goldhammer, over-the-counter drugs as well as prescription drugs.

Mr. GOLDHAMMER. That is right. It did not cover those over-the-counter drugs which were on the market prior to 1938 and were believed to be exempt from the efficacy requirements as well as safety requirements, the premarket clearance requirements. Is that correct?

Mr. HUTT. That is not entirely correct. If a drug was on the market prior to 1938 but another drug came on the market after 1938 with a related, similar, or identical ingredient and was the subject of an NDA, I would take the legal position that that NDA covered the earlier drug and, therefore, the grandfather clause would not apply.

Mr. GOLDHAMMER. I would agree that if a manufacturer came out with a new product for the first time, even though it imitated something on the market which was grandfathered, FDA would be justified in holding that to be a new drug.

Mr. HUTT. But, Mr. Goldhammer, what I am saying is that the fact that the NDA was issued after 1938 would be sufficient to break the grandfather clause for the pre-1938 drug, in my opinion.

Dr. GOLDBERG. It has not been litigated on that point.

Mr. HUTT. No. But I believe you can read that into the *U.S.V.* case the Supreme Court decided in June 1973, Dr. Goldberg. We have taken that position, I might add, in the preamble to the final hearing regulations which we published just roughly a year ago to implement the Supreme Court decisions.

Mr. FOUNTAIN. Do any of the members have any questions?

Mr. FUQUA. I have no questions.

Mr. FOUNTAIN. Congress gave the Food and Drug Administration some very potent enforcement tools to deter violations. Penalties can be severe, as we all know.

I would like to ask you, Mr. Hutt, whether you do not feel that the lawyer who notified you of the formulation change in the *Zerac Acne Gel* case would have had some second thoughts about another attempt to evade the new drug provisions of the law if you had told him in no uncertain terms that if the change in formulation still resulted in an illegal product, and they persisted in shipping it interstate, you would recommend that FDA apply the statutory sanctions of seizure, injunction, and prosecution?

Mr. HUTT. He knew that, Mr. Chairman. He was a very well-experienced attorney, an expert in food and drug law, and I would simply have been telling him the obvious. Whether in fact I told him that or not I cannot recall. I probably did.

Mr. FOUNTAIN. Did he know FDA would apply it?

Mr. HUTT. Certainly. That simply restates the law. Let me tell you the difficulty again, Mr. Chairman. I did a little research on this after our last discussion, to take a look at some of the cases on which affidavits have not been sufficient to go to summary judgment, and also the number of affidavits that have been required and the expertise of the people required for useful affidavits.

There are a number of cases, even after the *AMP* case you cited the last time, including one in the same judicial district, which have held that it is not sufficient for FDA to put in affidavits and that there must be a trial on the issue of new drug status.

The *Exedrin PM* case I cited the last time was in the same district, namely, the Eastern District of New York, as the *AMP* case, which was decided by the second circuit.

In that particular case we got affidavits from the following four witnesses:

Walter Modell, professor of pharmacology at Cornell, one of the world's experts on pharmacology; Dale Friend, associate clinical professor of medicine at Harvard Medical School, certainly an expert in the field; Raymond Houde, associate professor of medicine and pharmacology at Cornell; and Frederick Wolff, professor of medicine and head of pharmacology at George Washington School of Medicine.

The court held that was not sufficient to establish a lack of general recognition of safety. It said that where there is a genuine difference of medical opinion, some cases have said this very fact indicates a lack of general recognition. The court then stated that it would be unfair to drug manufacturers to conclude as a rule of law, that summary judgment would lie whenever the Government presents medical opinion stating that a drug is not generally recognized as safe and effective.

The conflicting affidavit must be examined, for not every conflict in medical opinion necessarily disproves general recognition.

The court ordered a trial. That is not the first case where that was done.

There are cases where we have had up to seven affidavits from prominent experts before we have been able to get summary judgment.

Now, telling the attorney on the other side of the *Xerac Acne Gel* case we could again seize, enjoin or bring criminal action would not scare him because he knew that with 200,000 products on the market we cannot bring, on a case-by-case basis, litigation against every one of them. That is again not why we should not enforce the law but why we had to find a new means of enforcing the law that would be effective for the first time.

Mr. FOUNTAIN. Is it your feeling we need a completely new rewrite of the law in this area?

Mr. HUTT. In my judgment; no. We have been able, with court sanction in these cases, to do a little better than Congress did in originally writing the law, to find a perfectly legitimate, lawful and acceptable means of enforcing the law without requiring a change in the statute.

Mr. FOUNTAIN. What proportion of FDA court actions would you say terminate in the agency's favor without a trial or contest?

Mr. HUTT. I can state that with some degree of precision, Mr. Chairman, because I have looked into that question; 99.7 of our seizure actions result in no litigation. What that means is this: They do not go to trial. They may well result in litigation to the extent that there are initial interrogatories and legal sparring before a consent order is negotiated, but only 0.3 percent of our cases actually go to trial.

That is to some extent misleading, because those 0.3 percent are the ones we are talking about here. They are the ones where there is something important from an economic standpoint riding on the case.

Mr. FOUNTAIN. I can appreciate to some extent the reasons for your actions when some of these situations arise. Yet, by not taking action against those new drugs on the market without an approved NDA, and letting the industry know that this is the policy or the way you will handle it, are you not in a way sacrificing the deterrent effect which normally flows from the desire of the manufacturer to avoid statutory sanctions?

Mr. HUTT. We are sacrificing the short term for the long term. We have two choices when you have a fixed amount of resources. You can take those resources and go on a case-by-case basis, and in the course of a year you might be able to affect 10 OTC drugs a year. Over 5 or 10 years, therefore, you would affect 50 or 100 drugs.

Or you can take those same resources and give up the short-term 10-a-year approach, and at the end of 10 years you will have affected 200,000. The decision we made was that the latter approach was far more in the public interest and was a far better use of resources.

Mr. DRINAN. What precisely is the short term you are giving up? Ten drugs a year? What harm do they do to the public?

Mr. HUTT. The kinds of cases we were bringing were not those which really involved harm to the public. They were more borderline cases of misbranding.

For example, we brought a number of cases against wrinkle-remover products on the ground they were new drugs, and not cosmetics. There was never any suggestion——

Mr. DRINAN. What are you sacrificing in the short run? We have to find out whether or not the consumer is being hurt. This, frankly, is a false dilemma you are trying to elaborate, that it is either/or. I don't think it is either/or.

Tell us more about the 10 a year. You say they don't hurt the public?

Mr. HUTT. In the *Zerac Acne Gel* case we were unable to show danger to health.

In the wrinkle-remover cases we were unable to show danger to health.

Mr. DRINAN. Are they ineffective?

Mr. HUTT. Our contention in the wrinkle-remover cases was that they did not remove wrinkles.

Mr. DRINAN. You have to tell me what you are sacrificing in the short term.

Mr. HUTT. What we are sacrificing in the short term is our ability, on specific wrinkle removers and hangover remedies and acne cases, to have them better labeled and better formulated.

Mr. DRINAN. That brings up the question of the delay in following through on the advisory committees, however. There does seem to be a very long delay. In the most recent case, weeks will go by before definitive action will be taken. Do you think that such delay is consistent with the statute?

Mr. HUTT. I am not sure, Father Drinan, what you mean by weeks are going to go by. We received the report roughly 9 days ago. Within a short period of time the Bureau of Drugs will have the recommendation to the Commissioner on that report.

It is a lengthy report and it does require some study.

I think Congress would be concerned if we were simply to implement an advisory committee report without reading, understanding, and analyzing it.

Mr. DRINAN. You had three oral reports from that committee prior to this?

Mr. HUTT. Yes. We said we could not just take an oral report. We needed something in writing, that I would use to go to court if, indeed, that is to happen.

Mr. DRINAN. I yield back.

Mr. FOUNTAIN. For whatever it may be worth, you had the panel's conclusions about 6 months ago.

Mr. HUTT. No; we did not. We went through that at the last hearing.

We had interim recommendations that at that point were subject to change, and, indeed, were changed.

Mr. GOLDHAMMER. With each meeting there is a memorandum sent to the Commissioner detailing in a page or two the most important developments during that meeting. Is that correct, Dr. Schmidt?

Dr. SCHMIDT. Yes, that is correct.

Mr. GOLDHAMMER. Do you see those reports?

Dr. SCHMIDT. Yes, sir, I read every one of them.

Mr. GOLDHAMMER. There was a report issued, I believe, on November 24, detailing rather explicitly the concerns the panel had about the zirconyl antiperspirant sprays.

As a consequence of that written statement the industry was given an opportunity in December to answer the statement.

I believe the record of the hearing held on April 23 will corroborate what I am saying.

In January the panel met again and decided that the information provided by industry in the December meeting, which was in answer to the November 24 written statement of the review panel, was not persuasive to justify a change in the panel's decision that it is still not generally recognized as safe, and it detailed at least seven reasons why they did not feel anything had been added by the December presentations of industry.

I believe a memorandum of that January meeting was prepared and I would recommend that it be placed into the record. The memorandum to the Commissioner is dated January 31, I believe, and the decisions of the review panel were again reiterated and the panel detailed at least seven reasons they felt this was not generally recognized as safe.

[The document referred to follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, FOOD AND DRUG ADMINISTRATION

TO: The Commissioner
FROM: Mary K. Bruch, Executive Secretary of Bureau of Drugs FDA OTC Antiperspirant Panel
SUBJECT: Eighth Meeting of the OTC Antiperspirant Panel—*INFORMATION ALERT*

The eighth meeting of the OTC Antiperspirant Panel was held at the Parklawn Building on January 30 and 31, 1975. All members, except Charles Evans, M.D., Ph. D. attended the meeting.

OPEN SESSION

There was no open session held. The announcement was made by the Chairman that anyone wishing to make a statement to the Panel could do so.

INFORMATION MEMORANDUM, OTC ANTIPERSPIRANT PANEL, EIGHTH MEETING, PARKLAWN BUILDING

PANEL MEMBERS

E. William Rosenberg, M.D., Chairman; Zenona Mally, M.D.; Charles Evans, M.D., Ph. D. (absent); Jane Rosenzweig, M.D.; Eli Shefter, Ph. D.; Robert Scheuplein, Ph. D.; and J. Wesley Clayton, Ph. D.

LIAISON MEMBERS

Consumer, Ms. Marsha Gardner; *Industry,* Robert Giovacchini, Ph. D.

FDA STAFF MEMBERS

Mary K. Bruch, Executive Secretary, Division of Anti-Infective Drug Products; Lee Geismar, OTC Staff; Joe Hussion, OTC Staff; Gary Yingling, General Counsel's Office; and Peter Hutt, General Counsel.

CLOSED SESSIONS

The Panel had been presented with a great deal of information at both the November and December meeting. Procter and Gamble made a new submission of data at the December meeting and also hand delivered additional information, including an outline of proposed studies, to Panel members two or three days prior to the meeting. Carter-Wallace had also made an additional submission. All these data involved zirconium-containing antiperspirant formulations.

The first hours of the meeting were spent in reviewing the material presented by Procter and Gamble on December 16, 1974. They discussed what has been done in response to the Panel's initial concern and what is proposed.

There was much discussion about the consequence of placement of these aerosol ingredients in Category II and III. The Panel concluded that it would be difficult

to say that there was general recognition of safety in light of all the experts heard by the Panel who were unwilling to say they thought aerosol application of these products was safe.

The Panel asked Mr. Gary Yingling to further clarify Category II and III and to clearly state the time course and effects of placement in one or the other of the categories. They were especially concerned about the problem of production control and identity of the complex ZAG.

The Panel spent a great deal of time reviewing the studies which have been done and especially what is known of the chemical structure of ZAG. The company has provided the outline of the production procedure but it is not clearly elucidated. The analysis often depends on Al/Zr ratios and pH measurement. The difficulty in control and analysis was stressed where the specific complex cannot be tested for or identified.

The intricacies of projecting low-dose, long-term exposure in man to higher-dose, short-term animal exposures was explored. The Panel is admittedly in a difficult area which involves many products used by the consumer. The basic risk is long-term effects from a repeated daily exposure as well as estimation of the amount of particles reaching the lung and deposited there. The burden to the body with possible exposure in the gastro-intestinal tract and the blood stream was outlined by the Panel.

This difficult decision by the Panel required much weighing of the risk/benefit rationales which have been spelled out in the Panel's Position Paper.

They asked Mr. Hutt to clarify for them his own view of Category II and what placement there would mean.

Mr. Hutt reviewed the three categories and then particularly addressed the problem of a novel compound which might have difficult analytical problems. His point was that if there are five products, all with ingredient X, which has a history of difficulties, but with closely controlled procedures, is shown to be safe in one manufacturer's hands, then to be generally recognized as safe and effective, a regulation would have to be written so that products which contain X would be as safe and effective as the first manufacturers. If such conditions of manufacture cannot be written, then an NDA would be required which would direct FDA to look critically at each product to show that each is as safe and effective as the original.

He also clarified the meaning of general recognition and told the Panel that they were representative of a variety of scientific groups and were acting in their place.

Mr. Hutt also re-emphasized the importance of risk/benefit by saying that if the benefit is nil then the risk would also need to be nil or less, if that were possible.

After further discussion the Committee made their decision on Category II by unanimous vote as follows: "All zirconium-containing aerosol antiperspirants/deodorants be placed in Category II".

Our decision was made for the following reasons:

1. Unnecessary incidence of bronchial and respiratory distress.
2. Unnecessary burden of zirconium particles on respiratory and gastrointestinal tract.
3. Likelihood of retention of zirconium particles in the lung.
4. Insufficient evidence that zirconium-containing particles in the body are not altered into substances of probable antigenicity.
5. Insufficient evidence of safety of long-term exposure to zirconium-containing aerosols.
6. Our assessment as to benefit-to-risk-ratio: Comparable degrees of perspiration control are achievable with other preparations which are generally recognized as having less potential for harm.
7. The chemical and physical complexities of zirconium-containing antiperspirant formulations preclude its being identified in a generic manner and therefore each company's product should be evaluated separately. The Panel believes the IND/NDA procedure would be required to achieve this.

The Panel believes that the major risks associated with the products, discussed above, are primarily those of long-term use. We do not believe users of these products are in imminent danger, since, at this time, we do not have documented cases of serious clinical disease. We see no need to suggest a product recall

The continued marketing of these products should be permitted contingent upon the vigorous pursuit of safety testing by industry. The Panel plans to provide guidelines for those tests it considers essential.

It is understood that the results of further studies (which should be pursued in a timely way) are of such concern that they will follow the results until they have made their report to the Commissioner and will recommend other actions if they feel they are required.

One central issue in their decision was that one manufacturer was able to produce effects in monkey lungs, in a 90-day study, with only slight alteration in the preparation and formulation of a zirconium-containing aerosol. The Panel felt that if this situation existed, the product should be considered not generally recognized as safe and effective and be subjected to the IND/NDA procedure so that the manufacturer would come under the New Drug inspection and controls regulations.

COMMENT BY EXECUTIVE SECRETARY

The Panel spent a long period of discussion prior to making their decision. They recognized the Commissioner's position as the recipient of many questions on this subject. They also recognized, and questioned the consumer liaison member about her view, that consumer advocates may believe a risk to the consumer still exists and may also feel that the Panel was pressured into retracting their former position in view of the course of their decisions on zirconium-containing aerosols.

The first aspect of this problem is decided but the question of aluminum aerosols still needs to be settled. Also the Panel still has to discuss effectiveness testing and labeling. Both subjects contain problem areas which really have not been addressed by FDA previously.

MARY K. BRUCH.

Mr. HUTT. Is that the one where they recommended that there was no need to expedite it and take it out of the normal course?

Mr. GOLDHAMMER. No. They did say they were not recommending that outstanding stocks of the product be removed from the market.

Mr. HUTT. My recollection is that they also recommended that that should not be taken out of the normal procedure and that it should proceed through the full OTC drug review procedure laid out in the Code of Federal Regulations whereby it would be included in their report and it would then be subject to all the normal procedures. They recommended that no immediate action should be taken.

Mr. GOLDHAMMER. Well, I understand——

Mr. HUTT. Is my recollection incorrect?

Mr. GOLDHAMMER. I do not have the memorandum.

Mr. THOMPSON. Are you talking about the January meeting?

Mr. GOLDHAMMER. The January memorandum to the Commissioner.

Mr. THOMPSON. There was language that there was no imminent danger to the public.

Dr. SCHMIDT. I have the quotes from the memorandum sent to me by the panel on January 31. That does state that their decision at that time was that all zirconium-containing antiperspirants be placed in category II. They go on, however, to say, "We do not believe users of these products are in imminent danger, since, at this time, we do not have documented cases of serious clinical disease. We see no need to suggest a product recall." They go on to say, "Continued marketing of these products should be permitted contingent on the pursuit of safety testing by industry." And the panel planned to go on and provide guidelines for those tests that it considered essential.

Mr. HUTT. So at that time, Mr. Goldhammer, it is true they were recommending against immediate action by the Food and Drug Administration.

Mr. GOLDHAMMER. Is the test for determining whether a product is a new drug, and therefore not eligible for interstate shipment unless it had an approved new drug application, the test of imminent danger to health?

Mr. HUTT. Again we are plowing ground we went over for at least an hour the last time. The fact is that the issue is whether one completes due process of law, as we discussed at great length last time, and you go through the entire administrative procedure, or whether you,

because of some health hazard, interrupt the normal procedure, take everything out of order, and do something on quite an emergency basis. The issue is not whether new drug status is contingent upon imminent hazard to health. Of course it is not, and we both know that.

The issue here was whether we would follow a published procedure that was laid out very carefully in the Code of Federal Regulations that has been endorsed by at least four or five courts which have looked at it now, including the U.S. Supreme Court, or whether we would throw that to the winds and adopt willy-nilly a new procedure out of thin air.

My judgment would be, absent some good solid health hazards, which we may have here—and that is the issue before us now—we would be thrown out of the courts if we did not follow our published procedure.

As you know, courts have held that a government agency must follow its published procedure unless there is some reason to vary from it, and it has to be a good reason.

Dr. SCHMIDT. I also point out that the health hazard that is being raised is not an immediate or imminent hazard. It is the consideration of whether or not this product over a long period of time with certain exposures can sensitize pulmonary tissues and give rise to pulmonary granulomas. The panel repeatedly said there is no evidence of imminent or short-term hazard.

Again I will remind you that last time we discussed this process we pointed out that on at least three occasions, when we thought there might be a safety hazard, the process was speeded up; for example, hexachlorophene was taken out of order and moved through the process ahead of the panel's full report.

This panel at the January 31 meeting elected not to ask me to take zirconium out of order. Until recently that was their decision and their recommendation.

Nine days ago I received a written report from them asking the contrary.[1]

Mr. HUTT. Mr. Chairman, the transcript of the meeting to which you made reference at the beginning of today's hearing will reflect that I laid out very carefully for the panel the alternatives they had at the March meeting.

Those alternatives—I have not seen that transcript but I remember fairly well what I said—were to allow it to go through the administrative process; to speed it up to the point of taking it out of order in the way that we did TBS; that is, at the time of their report to separate it out from their report and expedite its handling at that time; or to speed it up and not wait for their report but to make an immediate recommendation to the Commissioner.

They asked me at that time what I thought they should do, and I said that was not my job to advise them. We were asking their advice and their recommendation. It would be highly improper for me or anyone from FDA to interfere in their decisional process until they had made that decision.

[1] In this connection, the recommendation of the review panel as published at p. 24343 of the June 5, 1975, Federal Register, vol. 40, No. 109, is "Because conclusive testing to establish the safety of zirconium-containing aerosol antiperspirants might take years to accomplish, and because in that time millions of consumers would be unnecessarily subjected to risk, the Commissioner should take immediate steps outside of the normal OTC drug review process to stop movement of these agents in interstate commerce until the safety testing has been done adequately to secure the approval of an NDA."
The full Federal Register statement appears at pp. 262-294 of the appendix.

However, they had the options laid out for them very, very clearly at that time.

Mr. FOUNTAIN. Getting back to my question about the possible deterrent effect of doing certain things, let me cite an example of this that I am familiar with. In December 1970 this subcommittee conducted a very limited investigation to determine the extent to which new drugs were being marketed without NDA's. As a consequence of this very limited survey, the subcommittee referred to FDA two new drugs on the market without NDA's. One was a new formulation of Ayerst Laboratory's ophthalmic solution Epitrate, and the other was Smith Kline & French's cold remedy Ornex.

FDA took prompt action, I am pleased to report, to obtain early compliance. On January 11, 1971, FDA advised Ayerst Laboratories of its opinion that Epitrate was a new drug subject to premarket clearance. The firm acted promptly to discontinue distribution of the new product and, on February 26, 1971, recalled all outstanding stocks. I am placing a copy of Ayerst Laboratories' February 26, 1971, recall letter into the record.

[The letter referred to follows:]

AYERST LABORATORIES,
DIVISION OF AMERICAN HOME PRODUCTS CORPORATION,
685 Third Avenue, New York, N.Y., February 26, 1971.

IMPORTANT DRUG RECALL

Ayerst EPITRATE ® (epinephrine sulfate)

Gentlemen: Several months ago Ayerst Laboratories introduced a revised formula of EPITRATE, a product with which you are undoubtedly familiar. The revised formula contained the active ingredient, epinephrine, as the sulfate salt in place of the bitartrate. The bitartrate form of EPITRATE had been used successfully by ophthalmologists for approximately twenty years.

The Food and Drug Administration recently determined that the revised formula of EPITRATE is technically a new drug, and as such requires an approved new drug application, although controlled studies were conducted by a number of ophthalmologists prior to its introduction.

At the request of the Food and Drug Administration, Ayerst Laboratories is withdrawing the epinephrine sulfate form of EPITRATE, and replacing it with the original product which contains epinephrine bitartrate.

In the meantime, please *discontinue at once, all shipments of EPITRATE (epinephrine sulfate)*. We would also appreciate your returning for credit your existing inventory, at your earliest possible convenience, to:

Director of Production
Ayerst Laboratories, Inc.
Rouses Point, N.Y. 12979

Please note on the outside of the mailing container—EPITRATE RETURNS.

On March 4, 1971 we will send you, based upon your purchasing history, an adequate supply of EPITRATE (epinephrine bitartrate 2%). This will be shipped by the fastest possible means so that you can continue to supply your accounts. You will be billed at the usual discount.

We sincerely regret any inconvenience to you and appreciate whatever assistance you can offer in order to make this exchange expeditiously.

Yours truly,

H. K. ROBERTS,
Vice President, Marketing.

Mr. FOUNTAIN. So, in little over 2 months from the time the subcommittee referred the violation to FDA, complete correction had been effected, including recall of all outstanding stocks. You will agree with me, I am sure, that that is efficient, effective, and economical enforcement.

Mr. HUTT. Do you have the facts on the *Ornex* case?

Mr. FOUNTAIN. I will get to that next.

Mr. HUTT. Good.

Mr. FOUNTAIN. The question I want to ask to follow up the prefaced remark—don't you think that that type of enforcement consistently used would pay off in greater compliance?

Mr. HUTT. I do not.

Mr. FOUNTAIN. You do not?

Mr. HUTT. I clearly do not. Our entire past history has shown that, with rare exception, and that may be a single rare exception, it has not paid off at all, and indeed resulted in the mess that we had to straighten out with the OTC review.

It was reliance upon that kind of approach that resulted in the fact that we have 200,000 OTC drug products on the market, but a total of only about 450 or maybe 500 new drug applications, meaning that there are virtually 200,000 unregulated products out there, and nothing to protect the public. That is why the old approach, the case-by-case litigation approach, was so totally ineffective.

Mr. FOUNTAIN. But Epitrate was a prescription drug.

Mr. HUTT. Yes.

Mr. FOUNTAIN. There were other prescription drugs being put on the market without preclearance. Is that right?

Mr. HUTT. Prescription drugs are quite a different issue. I would agree with you that there is greater effectiveness of the NDA system in the prescription drug field of that.

I think I can give you an illustration of the figures. During the period 1938 to 1962 we had roughly 8,000 new drug applications for prescription drugs.

During that same period we had less than 500 new drug applications for OTC drugs. Yet, as you know, there are many, many more OTC drugs that were marketed during that time than prescription drugs.

Mr. FOUNTAIN. Any questions, gentlemen?

Mr. THOMPSON. Mr. Hutt, with the adoption of the OTC monograph, are case-by-case actions precluded?

Mr. HUTT. No. We laid down a general rule that we would continue the case-by-case litigation approach whenever there was a health hazard.

Father Drinan, I should have mentioned that to you to alleviate your concern.

If there is a health hazard we will do one of two things. We will, as the Commissioner said, take an issue out of turn in the OTC drug review and deal with it on an expedited basis, or we will bring a lawsuit.

Similarly, if there is patent fraud—I think I mentioned at the last hearing a cancer quack which could, because of its effectiveness, also be considered unsafe or just a gross fraud on the public—we will take court enforcement action there.

Mr. THOMPSON. If you were to take a case-by-case method, your research and data base for proceeding would have to be quite thorough, would it not?

Mr. HUTT. Yes.

Mr. THOMPSON. Not unlike the type of information you would need from an OTC panel if you were to promulgate a series of regulations.

Mr. HUTT. I would say it could be done more quickly, Mr. Thompson, but it has to be good enough to win in court.

I have said many times that I do not believe just in litigating; I believe in litigating to win.

Mr. THOMPSON. What would be the detriment and possible penalties to FDA if a case-by-case method is taken and you erroneously seized a product?

Mr. HUTT. We would lose the litigation. If we were not well prepared we would get very bad precedent. That has happened on occasions in the past, where there is one product out of a series of products which, in effect, has immunity over a period of time because we have seized it and lost.

Mr. THOMPSON. That could have a detrimental effect on subsequent actions?

Mr. HUTT. Indeed it could. It would make it very difficult to bring seizure actions against competing products as well.

Mr. THOMPSON. Particularly in a specified line or type of product?

Mr. HUTT. Yes. We brought a case against a product called Ayds, a so-called reducing product, which we concluded was ineffective. We lost that litigation, and since then we have been unable to adequately control that type of product.

Mr. DRINAN. I take it that the FDA was wrong, then. The product was ruled effective and safe in the *Ayds* case?

Mr. HUTT. In our judgment, although we lost the litigation, we believe to this day we were correct in that litigation.

As I am sure you understand, you win a few and you lose a few on a case-by-case approach.

Mr. DRINAN. You cannot really fault a case-by-case approach by saying it is ineffective because in this case the judge presumably found evidence that was contrary to what the FDA found. Did you appeal the case?

Mr. HUTT. I cannot state with certainty whether we did or did not. Mr. Goldhammer, do you recall?

Mr. GOLDHAMMER. That case was thrown out on grounds of res judicata. The Federal Trade Commission brought a case with regard to false advertising. They apparently put on a case which was by no means a good one from the standpoint of the court. As a matter of fact, the court ruled that there was not even a scintilla of evidence put on by the Federal Trade Commission.

Then the FDA came along and filed a case, and, in effect, was thrown out because this question already had been decided—it was res judicata involving another arm of Government.

The Food and Drug Administration might have been able to put on a very persuasive case and may have won if it had not been for the fact that another court had ruled in another case involving another agency on the same issue.

Mr. HUTT. My recollection is that in one of those court decisions involving a reducing product we lost it on the merits. I would have to go back.

Mr. GOLDHAMMER. Yes.

Mr. HUTT. I think you would agree with me that when you lose one you are in a very difficult position when you start going against the others. That, indeed, is part of the problem with the wrinkle-remover decisions where we got some decisions out of the courts that really did not help us at all, whereas if we had gone on a rulemaking basis, established a clear administrative record, we could have achieved

uniform labeling for all wrinkle-remover products that I think could be upheld in the courts. That is now, of course, what we are trying to do.

Mr. FOUNTAIN. Are there products which remove wrinkles, or do they just cover them up?

Dr. SCHMIDT. There are some products that tend to remove the whole face. There are some products that burn and remove wrinkles that way, and I consider them extremely hazardous.

Mr. DRINAN. If I may follow up on a wrinkle in the thinking of Dr. Schmidt. He is downgrading litigation. I know how litigation goes on and on.

However, in the *Bentex* case, as I read it, the Supreme Court did not really confirm and bless and ratify everything you people are doing. It said group action, class action, is sometimes necessary, but it did not, as I read it, say it is futile to proceed on a case-by-case basis, at least at times.

I am wondering how this policy was formulated.

Dr. Schmidt, was it you who made this policy? Apparently you have concluded no case by case is warranted because if you lose a case, then it sets a bad precedent.

Did the whole Commission sit on that? Is there something written down as to an apparent policy not to go that route?

Dr. SCHMIDT. I would like to go back and answer a question of the chairman's that was never answered.

He said to our General Counsel, "Mr. Hutt, would it not be fair to say that you, Mr. Hutt, in a moment of frustration, decided to trade out these cases?" That question was not answered.

I shall answer it. It would not be fair to say that.

The necessity is to formulate some rational basis for handling just a massive problem; that is the regulation of the content, labeling and use of all OTC drugs which number into the hundreds of thousands.

As Commissioner of Food and Drugs I am responsible for the use of our resources, which are limited.

The decision was made to go the route of developing regulatory monographs which would control entire classes of OTC drugs, their formulation, their labeling, and that their ingredients were both safe and effective.

Mr. Hutt described the trading out of the cases involved. They are agreeing to conform with the monograph. The industry has shown willingness to abide by these regulatory monographs.

This is not in place of all case-by-case litigation by any manner of means. I assure you that we have done so in the immediate past and that we will continue to do so if there is evidence of a health hazard.

What Mr. Hutt was referring to was not "either/or" in the sense of no litigation of anything on a case-by-case basis but an entire monograph approach for everything.

The "either/or" is to try to get 400,000 OTC drugs into compliance. On a case-by-case basis, that job is just simply impossible.

Mr. DRINAN. I agree with that. Nonetheless, a monograph approach involves severe delays.

Dr. SCHMIDT. I will not accept that definition.

Mr. HUTT. No.

Dr. SCHMIDT. We may define the word "severe" and the word "delay" differently. However, you see there never has been a search

of the literature, a gathering together of evidence, testimony from the world's experts about the safety and efficacy of these ingredients. I will not accept anything but a sound, scientific, logical, rational approach that will hold up in court, and neither will anybody else.

Two years to look at hundreds of years of experimentation and literature and thousands of products and their ingredients is not a severe delay. These products have been on the market for literally scores and scores of years.

For the agency, in a relatively short period of time of 1, 2, or 3 years, to regulate in an effective way that entire mass of products, is a surprisingly short period of time and I think a great achievement.

Mr. HUTT. And, Father Drinan, in contrast with the case-by-case litigation approach, if we were again to try to attack the whole field on a case-by-case litigation basis we would be talking not about delay but we would be talking about never doing it.

You did ask one question, though, which I believe the Commissioner did not address directly, and that is how was the policy adopted.

There was initially brought into the Food and Drug Administration in the fall of 1971 a group of medical and other experts to discuss how we could go about regulating over-the-counter drugs. We presented some of our ideas to them and they responded in the course of a day's session.

Then in the Federal Register of January 5, 1972, we proposed the procedure that we are talking about at this time. We received comments on that, and in the Federal Register of May 11, 1972, we laid out a final procedure, together with, if I recall correctly, an 11-page preamble with 98 numbered paragraphs which discussed in enormous detail every comment which was made and how we reacted to that comment, whether we agreed or disagreed, and how the procedure was being changed. This, therefore, was not adopted in a closed room without public participation. It was adopted in the open democratic process which the law requires.

Mr. DRINAN. Elaborate a bit more if you will on what was said before; namely, that if there is any question on the safety of a drug the FDA does immediately proceed on a case-by-case basis.

How is the questionable safety evaluated or determined?

Mr. HUTT. I would like just to modify what you said in one small respect. We could not say if there is any question of safety that we would proceed on a case-by-case basis because there may well be questions in the sense that a panel would say "We would like to see someone run a further study," not that they are doubting safety but simply to confirm the safety.

In those instances, if we were to take everything out of order, once again there would be chaos and we would be back to the case-by-case litigation approach.

What we are talking about is where a panel says, "We think there is a health hazard and it is of a kind that you should act promptly."

When those are isolated and brought to our attention we will take action.

Mr. DRINAN. Tell me about the 99.7 percent of the seizures which are always successful.

Mr. HUTT. Those are the ones where we found hairs in food, and——

Mr. DRINAN. By "we" you mean the Commission and not the advisory panel?

Mr. HUTT. That is right.

Mr. FOUNTAIN. I think we all understand, but this is a good point to emphasize.

As I understand it, the Food and Drug Administration does not have the burden of proving the safety of new drugs. That is the burden of the manufacturer. Is that right?

Mr. HUTT. That is correct.

Mr. FOUNTAIN. In the case of Ornex——

Dr. SCHMIDT. We do have the burden of proving in court, however, that something should be removed from the market.

Mr. HUTT. We have the burden of proving it is not generally recognized as safe and effective.

Mr. FOUNTAIN. We understand that.

In the case of Ornex, again referring to an example where FDA acted expeditiously, you acted promptly and notified the firm, but in that case the firm refused to recall the product.

Mr. HUTT. That is right.

Mr. FOUNTAIN. FDA promptly had the product seized.

Mr. HUTT. That is right.

Mr. FOUNTAIN. Again, there appears to have been no agonizing about whether FDA had the manpower to bring the action. The seizure resulted in the court contest.

The court never was given the opportunity to rule on the merits of the Government's case because it was one of those where you, Mr. Hutt, apparently compromised it. You "traded" it out.

Mr. HUTT. That is the colloquial way of saying we reached a compromise.

I would like to mention one thing in that case so that the record is clear. I personally had nothing to do with that case. I told my staff if they wanted to litigate that case they could do whatever they wanted. That was because, while I never had any connection with it when I was at Covington & Burling, that firm had some connection with that case and I, therefore, totally disqualified myself on that case.

I am frankly not certain how that case was resolved. Mr. Yingling could correct me if I am wrong, but I recall hearing there was some change in formulation along with a stipulation that they would follow the monograph when the monograph came out.

I would have to have someone from the office provide something for the record on that because I never did inquire into it at all.

I would point out, though, one thing. It is my recollection that the court enjoined us from further seizures or from taking further action, or stayed further action on our behalf, or my predecessor agreed to it, in any event, through one form or another. So it was a totally meaningless type of case to have brought. It achieved nothing in terms of compliance.

Second, there were roughly at least a thousand, and some people said up to 2 or 3,000, competing products, all of which stayed on the market, were not changed in formulation, and have not been changed in formulation to this day.

This again illustrates how bringing one isolated lawsuit is absolutely meaningless in the real world.

Mr. FOUNTAIN. Let's see. Suppose you had let this case run its course and the FDA had won.

Mr. HUTT. Yes.

Mr. FOUNTAIN. The message would not have been lost on the drug manufacturer, and the industry as a whole. It might have had an impact on these 2,000 cases.

Mr. HUTT. Our experience is directly to the contrary, Mr. Chairman. We again, in the hangover cases, in the wrinkle-remover cases, in the *Xerac* case, it had no impact, the fact that we won. It had no impact whatever. Not one drug company changed its labeling, its advertising, or its formulation as a result of that.

I testified to that last week, Mr. Chairman.

Dr. SCHMIDT. This points up the importance of the blanket regulatory monograph which by its very nature forces compliance of the entire industry. I think it is naive to assume that people in this very highly competitive market will do any more than say, "Boy! I'm glad it was them involved in that case." For people to run and get in line when they did not have to, to conform to some court case somewhere in the country staggers the mind.

I think your point that this one case did not use up our resources is valid. We are not stopping case-by-case litigation. The point we are trying to make is that it would be impossible for us to do this same thing with very many cases. There are hundreds and hundreds of these products which are mislabeled, or illogically formulated—not dangerous.

A lot of people think that when something is categorized as not safe and effective that it means that there may be an imminent danger to health, that there is a safety question. However, it can be in this category because of mislabeling. It can be in this category because there is not substantial evidence of efficacy, with no safety question at all.

Dr. GOLDBERG. With respect to Ornex, which was promoted by the manufacturer as a new and superior drug at the time FDA initiated its action, I would submit that you will never know what the consequences of a successful FDA action might have been because the case was traded out.

I read the transcript of the court proceedings in Philadelphia in which the company was granted a temporary injunction. The basis for that was purely and simply, as I remember it, because the company had advertised to the physician rather than to the general public, and the court was persuaded that the manufacturer's reputation might be hurt if it was not given an opportunity to present its case on the merits with the product remaining on the market in the interim.

Mr. HUTT. That is right.

Dr. GOLDBERG. The judge said at the time he was not persuaded there was any merit to the manufacturer's contentions.

Would you submit for the record who actually made the decision?

Mr. HUTT. Yes.

Dr. GOLDBERG. Traded out this case and the reason for it.

Mr. HUTT. I would be happy to do that.

[The information requested appears in the appendix at p. 309.]

Mr. GOLDHAMMER. Mr. Chairman, I would like to have the opportunity of having the record reveal that I had been with the Food and Drug Administration from the days even before the enactment of the 1938 act. I think I am in a position to testify at this hearing on how the Food and Drug Administration operated in those days.

Mr. FOUNTAIN. You are not saying it was necessarily better.

Mr. GOLDHAMMER. I am saying that my experience is such that I have good reason to believe that it was better.

In the first place, even when I retired from the Food and Drug Administration at the end of 1964 we were a small organization. I do not believe that our total appropriation exceeded $50 million.

Mr. FOUNTAIN. How many employees were engaged in the operation at the time?

Mr. GOLDHAMMER. I cannot give you precise information on that. It may have been somewhat in excess—I cannot give you information on that. It was not a large organization, in any event.

In addition to that we had the responsibility for enforcing laws which are no longer the responsibility of FDA. For instance, drug abuse outside of narcotics was the responsibility of the Food and Drug Administration. This took large enforcement effort.

The Food and Drug Administration also had the responsibility for establishing tolerances for pesticides. This is no longer the responsibility of the Food and Drug Administration. That was an important and costly responsibility.

Whereas the Food and Drug Administration has added responsibility today, many of these added responsibilities are compensated for by the fact they have lost responsibility, important responsibility, for instance, in hazardous substances, for which today there is a wholly new agency.

The impression one would gather from the testimony of the witnesses from the Food and Drug Administration is that the Food and Drug Administration throughout its period of operation was in a helpless position, not able to enforce the law effectively.

However, up until 1964 when I left, the Food and Drug Administration was enforcing the law effectively.

Many, many actions were being brought. I think, Mr. Chairman, during the cyclamate hearing you introduced into the record the evidence of a disastrous drop in the number of regulatory actions which were being brought by the Food and Drug Administration. It was a fantastic drop, beginning around 1970, as compared to what it was in 1945 when the total appropriation of the Food and Drug Administration was about $4 million.

I was Director of the Division of Regulatory Mangement for many years, and an Assistant Director of the Division of Regulatory Management for many years prior to that.

Prior to my assignment to the Division of Regulatory Management it was called the Division of Litigation, which is a clue as to the kind of work this division did.

It was my responsibility to handle all court actions, once they were brought, if there was any intimation whatever of a contest.

I can tell you we had scores of cases, and records in the files of the Food and Drug Administration will bear me out, we had scores of cases running simultaneously. Most of these cases when contested, were won in court, We didn't run away from a contest. It was regarded as our everyday operational responsibility.

If it was necessary to bring a case we brought a case.

At any given time there were scores of cases which were active, for which we had to negotiate with attorneys, write interrogatories, take depositions, and do all the things necessary to prepare for a court trial.

Our ability to win cases greatly discouraged contests so that there were very few.

I can tell you that in deciding the kinds of cases that were to be brought, we considered not the individual drug but all of the drugs involved in the particular class of the drug we were proceeding against.

Mr. THOMPSON. Was there a case involving wrinkle remover?

Mr. GOLDHAMMER. Yes, the wrinkle remover cases were brought in at the tailend of my career. I had a hand in the consideration of those cases.

Some we won, some we lost.

Mr. THOMPSON. There are still wrinkle removers on the market.

Mr. GOLDHAMMER. Well, some we won, some we lost. It was a question of enforcement.

Beginning with around 1969 or thereabouts one can note a sharp drop in the initiation of cases. It is far more likely that failure to enforce the law engenders disrespect for the law and widespread violation of the law to the point where when you attempt to bring about a correction you have gotten yourself into a position where you have a mountain of cases to tackle.

However, that was not the situation in the early days of FDA. We kept current. As soon as the violation was encountered, if it was worthy of correction, action was undertaken, even if it meant going to trial.

Having won, then it was customary for the Food and Drug Administration to issue a notice to the entire industry. There were many notices to the industry that such products would be regarded as new drugs which required new drug applications. Implicit in that notice was that failure to comply would bring action if the case were more than just of a technical violation.

Mr. Chairman, I had to put that in lest we get the idea that the Food and Drug Administration was always an agency which did not act.

Of course, we always considered classes, We never considered an action on a basis of an individual action. Always in our discussion was, "What are we going to do about the others?"

Mr. FOUNTAIN. The subcommittee will take into account this period of time.

Mr. HUTT. I must respond to that very briefly.

Dr. SCHMIDT. The Defense Department looks different from how it looked in 1930. Science is so vastly different. The efficacy requirements were not implemented in 1964.

Mr. HUTT. I would have to respond that I am in total disagreement with Mr. Goldhammer. It was the lack of enforcement when he was in the Food and Drug Administration that requires us today to now correct the problem that we find in the marketplace.

I was in the private practice of law during the time that Mr. Goldhammer was supposedly enforcing the law. I knew as an attorney, and all of my fellow attorneys knew, that the Food and Drug Administration would talk big and do very little back in those days. That is why over-the-counter drug manufacturers marketed all these products during the 1950's and 1960's—because what they did was to look at the record of FDA. FDA was not bringing court enforcement action. They were not enforcing the law. They were letting thousands,

hundreds of thousands, of over-the-counter drug products on the market, every day, Mr. Fountain, without doing anything about it.

If you went and talked to FDA that is the story you got.

I would, like any attorney, look at the seizure actions every month, and then I would look at the list of newly marketed OTC drugs. For every thousand newly marketed OTC drugs you might find—might, possibly find—one seizure, but it was usually not that high.

So the message FDA was giving is that "We are not enforcing the law against OTC drugs." When I came to the Food and Drug Administration I decided it was time to start enforcing the law.

That is why we brought about the OTC drug review, to stop the lack of enforcement which had gone on for 20 years.

Dr. GOLDBERG. I have no vested interest in FDA before or after you came to the agency. Lest the record appear black and white, or white and black as the case may be, I would like to note that by just flipping through medical journals I have found new prescription drugs placed on the market without approved NDA's, and FDA seems to know nothing about them. They are regarded by FDA, as in the case of one I inquired about only last week, as new drugs put on the market without new drug applications. I am waiting to hear what kind of regulatory action FDA will take in this most recent instance.

I am not persuaded the agency has been turned around from something it might have been at some other stage in its development.

Mr. HUTT. If we want to get into the question of prescription drugs it raises different issues. It raises a new policy on abbreviated drug applications, when they are required, and so on, which we might want to get into in the future.

To get into it today would be trying to do too much at one time.

Mr. FOUNTAIN. I agree.

Dr. GOLDBERG. We certainly would like to review this situation.

Mr. FOUNTAIN. I agree.

Referring back to the Ornex situation, I am placing in the record a copy of FDA's letter of August 8, 1972, to the subcommittee reporting the outcome of the Ornex litigation.

[The letter referred to follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., August 8, 1972.

DELPHIS C. GOLDBERG, Ph. D.,
Professional Staff Member, Intergovernmental Relations Subcommittee, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR DR. GOLDBERG: This is in response to your request for a status report on litigation involving the drug Ornex. I apologize for this delay.

As you know, Smith Kline and French (SKF) introduced and began promotion of its new product Ornex in January 1970. When the Food and Drug Administration (FDA) discovered that Ornex was marketed without an approved new drug application, it asked Smith Kline and French for medical documentation which might support a conclusion that the drug was generally recognized as safe and effective for its labeled uses.

The data supplied by SKF was evaluated as inadequate, and the company was asked to recall its stocks of Ornex from the market. When it refused to voluntarily recall Ornex and cease distribution, FDA advised the company that it would clear the market by a program of seizure actions. One seizure was accomplished on February 19, 1971.[1] On February 26, 1971, SKF obtained a preliminary injunction restraining FDA from initiating further regulatory actions.[2]

[1] *United States* v. *An Article of Drug . . . Ornex*, Docket No. 223–71, D. N.J.
[2] *Smith Kline and French Laboratories* v. *Richardson, et al.*, Docket No. 71–387, E.D. Pa.

An appeal from the preliminary injunction was filed in the Third Circuit pursuant to 28 U.S.C. 1292(a) on the ground that the District Court lacked jurisdiction to enjoin FDA from conducting multiple seizures of an unapproved new drug under the doctrine of *Ewing* v. *Mytinger Casselberry, Inc.*, 339 U.S. 594 (1950), and on the further ground that the evidence before the District Court established as a matter of law that Ornex was not generally recognized among qualified experts as safe and effective for its labeled uses and was, therefore, a new drug.[3]

Thereafter, while awaiting the scheduling of oral argument on the appeal, FDA on February 5, 1972, published its proposal to promulgate regulations classifying over-the-counter drugs as generally recognized as safe and effective and not misbranded. (37 F.R. 85–89.) Because the proposal recognized that adequate consumer protection and "equitable enforcement of the law requires that the agency proceed against all manufacturers of similar preparations" rather than a selected few, manufacturers of OTC drugs involved in litigation were offered an opportunity to settle the litigation by stipulating that they will abide by the OTC monographs applicable to their preparations. SKF, aware of this policy, requested that it be accorded a disposition of its case consistent with that accorded to other OTC manufacturers involved in litigation. Consequently, a stipulation disposing of the three Ornex cases has been executed.

Pursuant to the terms of the stipulation, Smith Kline and French has reformulated Ornex by deleting the salicylamide and caffeine components and has agreed to make any other formulation and/or labeling changes necessary to comply with applicable OTC monographs; upon joint motion of the parties, the suit for injunction and consequent appeal have been dismissed and the injunction against FDA vacated; and, SFK having withdrawn its claim and answer in the New Jersey seizure, the seized stocks have been condemned under a default decree.

A copy of the stipulation is enclosed. If we may be of further assistance, please let us know.

Sincerely yours,

GERALD F. MEYER,
Office of Legislative Services.

Mr. FOUNTAIN. The mechanics of the trade out is suggested by this passage in FDA's letter:

> Because the proposal recognized that adequate consumer protection and "equitable enforcement of the law requires that the agency proceed against all manufacturers of similar preparations" rather than a selected few, manufacturers of OTC drugs involved in litigation were offered an opportunity to settle the litigation by stipulating that they will abide by the OTC monographs applicable to their preparations. SKF, aware of this policy, requested that it be accorded a disposition of its case consistent with that accorded to other OTC manufacturers involved in litigation. Consequently, a stipulation disposing of the three Ornex cases has been executed.

Mr. HUTT. Who signed that letter, Mr. Fountain?

Mr. FOUNTAIN. Gerald F. Meyer.

Mr. HUTT. This was not——

Mr. FOUNTAIN. August 8, 1972.

Mr. HUTT. This was not the letter to the company actually containing the stipulation?

Dr. GOLDBERG. This was an explanation to the subcommittee in response to our request as to what the outcome had been.

Mr. HUTT. All right.

Mr. FOUNTAIN. Since 1971 this subcommittee has brought to the attention of FDA a number of complaints from both industry and consumers about misbranded drugs on the market, as well as new drugs on the market without approved NDA's. For 3½ years FDA has told the subcommittee that no action would be taken, despite the misbranding or new drug violations, until after the monographs

[3] *Smith Kline and French Laboratories* v. *Richardson, et al.*, No. 71–1484.

had been published and had become effective. Presumably those violative products are still on the market, and immune from FDA action for an indefinite period—probably years. Is that right?

Mr. HUTT. I do not think for years. These undoubtedly were products which were not either patent frauds or health hazards, and therefore they fit into the general category of literally 200,000 products, all of which must be reformulated and relabeled at some point in time.

The question again is, do you take some out of turn? Is there good reason to do that or do you handle all on a scheduled systematic basis?

Mr. FOUNTAIN. I can, of course, appreciate the tremendous problem you have with respect to these over-the-counter drugs by the thousands, many of which have been on the market for many, many years.

However, I find, at least from my point of view and based upon the information I have, and that is the way we have to form our opinions, I find it disturbing that FDA now appears to have extended its moratorium on enforcing the new drug provisions from OTC drugs to prescription drugs. The subcommittee recently inquired about a number of prescription drugs on the market without NDA's. We received a reply with two enclosures dated March 28, 1975. I am placing in the record the letter from FDA and one of the enclosures. The other enclosure appears at pages 91–92.

[The documents referred to follow:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., March 28, 1975.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations and Human Resources, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: This is in response to the telephone request of February 20, 1975, by Mr. Goldhammer, Consultant to the Subcommittee, for information on several drugs.

Enclosed is the data requested by Mr. Goldhammer on the following drugs:

Triafed	Allerfin	Action C
Allerphed	Triprofed	Actacin
Triacin	Action	Actacin C

Also enclosed are *Federal Register* publications referenced in the attachment from the Bureau of Drugs as well as correspondence between the Agency and Burroughs Wellcome and Company on this matter.

If we can be of further assistance, please let us know.

Sincerely yours,

ROBERT C. WETHERELL, Jr.,
Director, Office of Legislative Services.

Enclosures.

DRUG STATUS

1. Are the identified drugs prescription or over-the-counter (OTC) drugs?

The listed drugs, Triafed, Allerphed, Triacin, Allerfrin, Triprofed, Action, Action C. Actacin, and Actacin C are all prescription drugs.

2. Are these drugs subject to new drug applications (NDA's)?

While they are subject to the NDA requirements, we have permitted such products to remain on the market under the aegis of the prime NDA until such time as final resolution is made. Consequently, we have not taken action against products under this category pending completion of separate reviews by the OTC Panel on Cold, Cough, Allergy, Bronchodilators and Antiasthmatic Drugs and the FDA Advisory Committee on Drugs Used in Allergy, provided that they meet the requirements for continued marketing as described in the *Federal Register*

notice of December 14, 1973. Please see the *Federal Register* announcements of May 15, 1973, December 14, 1973, and the incoming letter from Burroughs Wellcome and our response to same, attached, which goes into more detail in this matter.

3. Are these drugs listed under the Drug Listing Act?

Of the drugs mentioned above, only Action marketing by Michigan Pharmacal, and Actacin marketed by Diacin Chemical Company, are regarded to be in compliance with the provisions of the Drug Listing Act. A compliance program specifically designed to assure compliance with the Drug Listing Act by all drug firms marketing human drug products will issue shortly.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., March 4, 1975.

Mr. CLEALAND F. BAKER,
Burroughs Wellcome & Co.,
3030 Cornwallis Road,
Research Triangle Park, N.C.

DEAR MR. BAKER: This is in reply to your letter of January 31, 1975, expressing your concern regarding the marketing of products similar to Actifed and Actifed C preparations without clearing FDA's "regulatory procedures."

At the present time the ingredients found in your products (triprolidine HCl and pseudoephedrine HCl) are being reviewed by the OTC Panel on Cold, Cough, Allergy, Bronchodilator and Anti-Asthmatic Drugs and an FDA Advisory Panel on drugs used in allergy.

As you probably know there are a number of ingredients present in both OTC and prescription cold, cough and allergy preparations currently being marketed. Appropriate formulation and labeling of OTC drugs for these uses as well as the division between OTC/Rx is being considered in detail since the final OTC monograph which emerges from this review will have a substantial bearing on the formulation and labeling of Rx as well as OTC drugs used for these purposes.

FDA policy in this regard was published in the *Federal Register* of May 15, 1973, (copy enclosed) which specifies the interim guidelines for the formulation and labeling of prescription drugs intended for cough and allergy purposes pending the OTC drug monograph. On the basis of public hearings held on June 4, 1973, the Commissioner concluded that it was premature to adopt guidelines on the labeling of these prescription drugs. Since the issues involved in the OTC drug review are so closely related, and sound medical practice requires consistent formulation and labeling for these two types of products, it is essential that they both be subjected to new requirements at the same time. The Commissioner submitted the full record of the hearing for the prescription products to the OTC advisory review panel for its consideration in preparing its report on this category of drugs.

In view of the above, the Commissioner concluded it was appropriate to add currently marketed prescription cough and allergy preparations similar to or containing ingredients also in OTC cold, cough or allergy products to the list of drugs which may remain on the market beyond the applicable time limit for implementation pending review of all relevant scientific data for the OTC drug products. Please see the enclosed Federal Register notice of December 14, 1973.

Thus, at the present time, a firm may market a product falling under the scope of this drug category as follows:

1. In addition to the usual mandatory labeling requirements the current labeling should bear the required disclosure of drug efficacy study evaluations in the labeling and advertising as set forth in Regulation 21 CFR 3.81.

2. A firm which does not wish to disclose the drug efficacy study evaluation as required by 21 CFR 3.81 may follow the proposed interim guidelines, per Federal Register announcement of May 15, 1973. While this exemption does not apply to certain ingredients as listed therein, the guidelines do provide for the interim marketing of a product which contains an antihistamine and a nasal decongestant limited for use for the treatment of seasonal and perennial allergic rhinitis and vasomotor rhinitis, subject to review under the ongoing OTC study of such products.

We note that the proposed interim guideline of May 15, 1973 does not permit the marketing of preparations offered for cough containing antihistamines and oral decongestants such as found in Actifed-C.

3. Additionally, as with all drugs, we require that the products are manufactured in conformity with current good manufacturing practice.

We also wish to point out that the Federal Register of July 27, 1972, and February 9, 1973, makes no requirements for the submission of an NDA/ANDA at the present time since only those DESI notices dealing with a fully effective drug contains the conditions under which such drug(s) may be marketed.

We regret the delay concerning your submission with respect to the one-gallon size container for Actifed Syrup. In explanation, the responsibility for the review of this class of drugs was transferred from the Division of Cardio-Renal Drug Products to the Division of Surgical-Dental Drug Products. Also, our information is that the required stability data for the product was submitted only this month. We have been advised that a review of this material is completed and that a response to you will be issued soon. Should you wish to inquire further about the status of this review, you may contact the Division of Surgical-Dental Drug Products (HFD–160).

We recognize that there are situations where an NDA holder may, for a time, bear an inequitable burden as a condition for marketing a particular drug while related drugs are being marketed without such constraints. However, until a final order is published in the Federal Register withdrawing approval of the prime NDA, we are not in a position to institute a class action directed towards removing related drugs from the market.

Sincerely yours,

J. RICHARD CROUT, M.D.
Director, Bureau of Drugs.

Mr. FOUNTAIN. It is clear from these documents that the moratorium now cuts across the entire drug market, including prescription drugs. What is your comment on that?

Mr. HUTT. Mr. Fountain, I believe I mentioned earlier if we want to get at all into detail on the abbreviated or full NDA, or old drug, issue for prescription drugs, we should devote at least a couple hours to it. We would be happy to do that.

There is a proposed Federal Register notice—in fact, a total of five or six Federal Register notices that are in final draft form, which will appear in the Federal Register, dealing with issues of bioavailability, bioequivalence, and abbreviated drug applications, in the relatively near future.

Mr. FOUNTAIN. I am talking about drugs on the market without any NDA.

Mr. HUTT. They may be old drugs.

Mr. FOUNTAIN. New drugs.

Mr. HUTT. Who said they were new drugs?

Mr. FOUNTAIN. We will develop that as we go along. There are new drugs on the market.

Mr. HUTT. Mr. Fountain, again would you like to get into all of this?

Mr. FOUNTAIN. We will get into it.

Mr. HUTT. Right now?

Mr. FOUNTAIN. Stick around long enough.

Mr. HUTT. OK.

Mr. DRINAN. I wonder whether Mr. Hutt would agree FDA extended its moratorium from OTC to the others. Would you quarrel with that?

Mr. HUTT. Yes, indeed, Father Drinan, I would. I think what has happened is that we have begun for the first time to try to look at the issue of what, in the prescription drug area, is a new drug and a no longer new drug—or old drug, as we call it. We are in between switching from one system of regulatory control to another. We can get into all the details of that if the subcommittee wishes.

Mr. DRINAN. Concerning validity of the moratorium language, nonetheless there is a delay, shall we say. In switching from one way of doing business to another, you have a lapse of time. I raise the question as to whether or not the intent of the act is really being carried out.

The FDC Act says the public is supposed to be protected until the safety and effectiveness have been shown.

Do you feel that in the switching from, as you characterize it, the case by case to the advisory committee, do you think the act is really being carried out, the basic intent of the act, which is to protect the public until the safety is established?

Mr. HUTT. Yes; I do. As I pointed out, in the over-the-counter drug area, if we can stay with that a moment, all of these products are on the market. We do not have the ability tomorrow to go out and take 200,000 products off the market.

We are dealing with a situation we did not create, which was created in the past.

Mr. FOUNTAIN. They are the ones Mr. Goldhammer let get on the market?

Mr. HUTT. That is correct.

Mr. DRINAN. Of these 200,000, how many of those were grandfathered in? How many do you actually have jurisdiction over? How many of those did, in fact, get an NDA?

Mr. HUTT. This is a good example of what we have tried to do to repair damage which was done by the Congress to our enforcement capability.

In both 1938 and in 1962, Congress exempted from the new drug authority certain types of drugs, the so-called grandfather provisions.

We have established a rulemaking procedure which makes that distinction irrelevant. We are not only defining what is a new drug and an old drug, we are also defining what is misbranded. We are not distinguishing between a pre-1938 drug and a post-1938 drug.

We can do that in a way, therefore, which makes the grandfather clause irrelevant, and in effect takes public protection one step further, and a major step further.

Mr. DRINAN. You have jurisdiction over all of the 200,000?

Mr. HUTT. We do. The grandfather clause grandfathers only from the new drug provisions of the law and not from the adulteration and misbranding provisions.

Mr. DRINAN. Would you respond to the other part of the question? How many have in fact received——

Mr. HUTT. No one knows. As to NDA's between 1938 and 1962, there were 420 NDA's which went through the NAS/NRC review. There was an additional number we have never counted which simply dropped by the wayside because they had become obsolete. Therefore, in 1966, when the National Academy of Sciences looked at this issue, they looked at 420 drugs as contrasted with the hundreds of thousands which were on the market.

How many were grandfathered we have no way of knowing. It would be impossible to tell.

Dr. GOLDBERG. When you say no one knows, are you not authorized to maintain a register of drugs under the Drug Listing Act?

Mr. HUTT. We are. The Drug Listing Act of 1972 requires this.

Dr. GOLDBERG. Why would you not know from your register what drugs are out there if you are enforcing that act?

Mr. HUTT. The question put to me, Dr. Goldberg, was whether I knew how many were grandfathered?

Dr. GOLDBERG. And how many were NDA'ed. That was another question.

Mr. HUTT. We can go back. I said how many were NDA'ed, 420.

Dr. GOLDBERG. In your response to Father Drinan you made mention of drugs which had been on the market and dropped out.

Mr. HUTT. We can count those.

Dr. GOLDBERG. I understood you to have said nobody really knows what is out there. I am asking why you do not know.

Mr. HUTT. I said we did not bother to go back and count the number of once-effective NDA's between 1938 and 1962 for OTC drugs which became obsolete and which we revoked.

Dr. GOLDBERG. That is irrelevant in terms of what is on the market today. If products are no longer around why would you worry about them?

Mr. HUTT. I was answering the question put to me. That is why we did not count them.

Dr. GOLDBERG. Perhaps I misunderstood.

Mr. DRINAN. I don't think so. Perhaps we can rephrase it. Of the new OTC drug products coming on the market how many appear without any preclearance at all from the FDA?

Mr. HUTT. I would not be able to give you an answer today, Father Drinan. I would assume the vast, vast majority of them.

If someone puts out yet another aspirin product in a 5-milligram tablet there is no new drug application for that. There is no question.

There are 8,000 antacid products on the market today in rough terms. We had new drug applications for, between 1938 and 1962, and I would say subsequently, roughly 10 out of those 8,000.

That will give you an idea of the dimension.

Mr. DRINAN. With regard to the one advisory committee which has finalized its work and is operational regarding antacids, tell us about the effectiveness of its decrees.

Mr. HUTT. There has been total compliance, 100-percent compliance, without one piece of litigation.

Mr. DRINAN. Thank you.

Mr. FOUNTAIN. One of the two enclosures to which I referred earlier is a copy of an FDA March 4, 1975, letter to Burroughs Wellcome Co. The letter, on January 31, 1975, had expressed concern about the marketing of new drugs by some manufacturers without FDA preclearance, and to complete the picture I am placing in the record an April 8, 1975, reply to you, Dr. Crout.

[The letter referred to follows:]

BURROUGHS WELLCOME CO.,
Research Triangle Park, N.C., April 8, 1975.

J. RICHARD CROUT, M.D.

Director, Bureau of Drugs, Food and Drug Administration, 4600 Fishers Lane, Rockville, Md. 20852

DEAR DR. CROUT: Your letter of March 4, responding to our January 31 letter expressing concern about the marketing of products similar to ACTIFED® and ACTIFED-C® without clearance through FDA's regulatory procedures, has been carefully reviewed. Your response was not unexpected. We are aware

that, for some time, FDA has pursued a policy which permits introduction of new products, similar to recognized NDA products, without requiring adherence by the new producers to clearance procedures mandated in the Food, Drug and Cosmetic Act.

It may be administratively expedient for FDA to permit a bypass of any regulation which it chooses not to enforce, but the Agency mandate to protect the public against potentially dangerous products, or products which may not meet quality standards, is certainly not carried out through this policy.

At the time of our January letter, addressed to Dr. John Jennings, Associate Commissioner for Medical Affairs, our supplemental NDA for the clearance of a one-gallon bottle size of ACTIFED Syrup had been held up for the better part of a year. The particular concern communicated to us was the need for additional storage and aging data to further document the stability of the product in a gallon glass bottle identical in composition to the approved container for the commercially available pint size. Eleven months stability data was required to be submitted before approval was finally obtained, and we were required to use a 24-months expiration dating.

Previously, our Quality Control Laboratories had rejected the use of plastic containers because stability data was not satisfactory. However, some of the products which are presently being marketed, apparently without FDA clearance, are packaged in plastic containers without expiration dating. Do you have data on file demonstrating the stability of these formulations in plastic containers that we can compare with our own study results?

I would like to raise several questions about other specific points in your letter:

On page two in the first paragraph you state, "The Commissioner concluded it was appropriate *to add* currently marketed prescription cough and allergy preparations similar to and containing ingredients also in OTC cold, cough, or allergy products." The words "to add" seem to imply a deliberate action on the part of FDA—that the addition of these products has been carried out through the normal FDA review and surveillance. It would follow that, although the need for an NDA had not been enforced, FDA had, through its inspection procedures, assurance that the manufacturer was observing good manufacturing practices before the products were marketed.

Page two, numbered paragraph three, further stated, "Additionally, as with all drugs, we require that the products are manufactured in conformity with the current Good Manufacturing Practice." We would like to receive information available under the Freedom of Information Act covering the reports of FDA inspections which provided assurance to you that these products are, in fact, manufactured under appropriate Good Manufacturing Practices, and the stability data demonstrating that these products will maintain their potency in commercial use as packaged.

Page two, paragraph two under number 2, of your letter states, "We note that the proposed interim guideline of May 15, 1973, does *not* permit the marketing of preparations offered for cough if they contain antihistamines and oral decongestants such as found in ACTIFED-C®." However, the price lists of four of the generic manufacturers named to you in our letter indicated they were offering generic ACTIFED-C, despite the guideline.

If, in fact, the May 15 guideline is FDA's justification for adding certain formulations which adhere to labeling specified therein, it should follow that formulations or indications not included in the May 15 guideline, or covered by NDA's, would not be acceptable prior to the clarification of the status of all cough and cold products in the monograph to be published following the recommendations of the OTC Cough and Cold Panel.

It is obviously true, as stated in the last paragraph of your letter, that NDA holders bear an inequitable burden as a condition for continued marketing while later market entries are permitted to be sold without such constraints. The prime concern, however, in this situation is not the inequitable treatment of the respective manufacturers, but whether the Food and Drug Administration is, in fact, carrying out its mandate to insure appropriate formulation, manufacturing, and packaging of prescription drug products. Public proclamations by responsible FDA staff members give assurances to both professional and lay audiences that the FDA surveillance procedures insure the quality of *all* prescription products, particularly in the interchangeable group. The policy as enunciated is highly inconsistent with the negation of need for surveillance as actually practiced by FDA with respect to speculative generic market entries.

Sincerely,

CLEALAND F. BAKER,
Vice President, Corporate Planning.

Mr. FOUNTAIN. I quote from the last paragraph of this letter:

It is obviously true, as stated in the last paragraph of your letter, that NDA holders bear an inequitable burden as a condition for continued marketing while later market entries are permitted to be sold without such constraints. The prime concern, however, in this situation is not the inequitable treatment of the respective manufacturers, but whether the Food and Drug Administration is, in fact, carrying out its mandate to insure appropriate formulation, manufacturing, and packaging of prescription drug products. Public proclamations by responsible FDA staff members give assurances to both professional and lay audiences that the FDA surveillance procedures insure the quality of all prescription products, particularly in the interchangeable group. The policy as enunciated is highly inconsistent with the negation of need for surveillance as actually practiced by FDA with respect to speculative generic market entries.

I recognize that there are times when an agency cannot proceed against all violations. However, I believe most of us in Congress realize that an agency should establish priorities so that the public will get the maximum protection within limits of funds.

As a general rule, it seems to me, it would appear prudent—and, perhaps, this is your policy. As a matter of fact it was my policy in the practice of law, whether plaintiff or defendant—to handle, first, the most serious violations. In my opinion, the correction of violations which adversely affect public health, or which may adversely affect public health should be given the highest priority.

Would you agree with that?

Mr. HUTT. We certainly do. That is what we have been doing.

Mr. FOUNTAIN. Enforcement action against those violations involving the marketing of new drugs without NDA's establishing their safety, it seems to me, should also merit very high priority. Is that right?

Mr. HUTT. Only if, in fact, it is a high priority issue. If safety is regarded as not a problem for the product then that would not be a high priority issue.

Mr. FOUNTAIN. You have no way of knowing unless NDA's are filed.

Mr. HUTT. That is not necessarily true. If it is what we sometimes call a me-too product, and it is no different from 50 other products on the market, then there is no safety issue involved unless we have some reason to believe that there is a difficulty, in which case we would take action.

Dr. GOLDBERG. Just looking at the zirconium aerosols as a case in point, it seems to me that if FDA had actually accepted the application for review, and had determined whether or not the Procter & Gamble products were safe, they might not have been placed on the market and FDA's dilemma with respect to making a determination as to how to treat these products in view of their potential health hazard could have been avoided.

With further reference to the chairman's point, we must ask whether premarket approval is required by the law and also whether it is good policy when new types of products—and that certainly was a new type of product in terms of its manner of delivery—are being offered to the public that a determination be made, on the basis of the scientific evidence, as to whether or not they are indeed safe and effective.

Mr. HUTT. That particular NDA to which you refer was an abbreviated NDA. It was based upon the conclusion of the National

Academy that zirconium was safe. What P. & G. was simply doing there was not the kind of thing you are suggesting, Dr. Goldberg, of——

Mr. FOUNTAIN. You mean safe for roll-on.

Mr. HUTT. They were submitting an abbreviated NDA for the aerosol product based upon the conclusion of the National Academy that zirconium in a roll-on and cream were safe.

Dr. GOLDBERG. They were not applying for roll-ons, but rather for an aerosol form that could affect the products.

Mr. HUTT. That is right.

Dr. GOLDBERG. They went the proper route, in my judgment, in making an application to FDA so you could determine whether the product was safe and effective.

How could you conceivably know, without animal testing, whether or not the zirconium, when put into aerosol form, had any potential danger for the lungs or any other organ of the human body?

Mr. HUTT. You can say that about virtually every OTC drug on the market these days or which came on the market 10, 20, 30, or 40 years ago.

Dr. GOLDBERG. Precisely.

Mr. HUTT. What you are doing is using hindsight, which I have used with Mr. Goldhammer a little while ago, my hindsight saying he allowed all those products on the market.

I am sure he could use hindsight and say somebody 40 years before he got there allowed all those products on the market.

Dr. GOLDBERG. Not at all. I couldn't disagree with you more, Mr. Hutt. While I use the zirconium aerosol as a case in point, the principle is one we have been talking about for the last 5 minutes—whether or not a new type of product which has not previously been screened for safety and effectiveness, and I submit that zirconium in aerosol form is a new-type product, ought not to be precleared. In fact, does not the law mandate that it be precleared, either by an NDA or an ANDA? Certainly scientific evidence has to be reviewed.

Mr. HUTT. We are not determining that, Dr. Goldberg. That is the entire purpose of the OTC review. We are right back in the circle of discussion to where we were the last time we appeared here.

Dr. GOLDBERG. The fact remains that you avoided an opportunity to review this particular product, the aerosol spray, when the manufacturer submitted an application.

Dr. SCHMIDT. That is not correct. What we said was that that review would be done by the OTC panel. I would remind you——

Dr. GOLDBERG. We are talking about a time frame, an action which could have been taken, a product which might well have been kept off the market several years ago. Moreover, your procedures for due process might permit it to remain on the market several years more.

Mr. HUTT. That is what we are determining now. We cannot prejudge that issue because it is an issue which is now before the Commissioner.

Dr. GOLDBERG. I am not asking you to prejudge it. I am differing with your concepts of law enforcement and of your responsibilities under the law in turning this over to a panel rather than acting on an application which a company presumably in good faith put before you.

Mr. HUTT. As my late father used to say, "that's what makes horse races."

Mr. FOUNTAIN. I have a prepared outline of questions, Dr. Schmidt. If a panel has placed a drug in a given class of drugs into category II, but the final monograph of that class has not yet been published, and a firm wants to market that drug with the category II label for the first time, is the firm free to market the product without filing an NDA or will FDA require the filing of an NDA prior to marketing?

Mr. HUTT. If I understand you correctly, there is a report by the panel that it is in class II, and that has been published as a proposal in the Federal Register.

Mr. FOUNTAIN. That is right.

Mr. HUTT. It is before the final monograph. Why anybody would ever do it is utterly beyond me, but the fact is—yes, they are free to market that product for the couple of months they could market it until they would have to take it off the market.

What we are finding is literally just the opposite, because people are not irrational. What we are finding is that the minute that a report is available in draft form the manufacturers are taking off the market those which are in category II, and they are marketing products which are in category I because they want to get on the market as fast as they can something which is safe, effective, and properly labeled.

Your hypothetical question is simply totally unrealistic. It has not happened, and I could not conceive of its happening.

Mr. FOUNTAIN. I am not so sure I agree with you. However, I shall ask this. What about category——

Dr. SCHMIDT. Is there an example? I would love to hear an example.

Mr. FOUNTAIN [continuing]. Category III drugs. I was asking the hypothetical question based upon this background of information which we have and which we have been exploring.

What about category III drugs? Would a manufacturer, who wants to market a drug for the first time with claims which are placed in category III by a review panel, and excluded from the monograph but permitted to be used in labeling for, say, a 2-year period, be required by FDA to file an NDA?

Mr. HUTT. No, sir, he can come on the market with the same restriction as someone who was on there since 1890.

Mr. FOUNTAIN. During the 2-year period?

Mr. HUTT. Yes, during that 2-year period, as agreed by the U.S. district court in the District of Columbia, he is subject to the same restrictions, rights, and benefits as anyone else under the review procedure.

Those are products for which there is no health hazard, Father Drinan, again to go back to your earlier concern.

Mr. DRINAN. Does the statute and the whole history of it justify the distinction you continually make between safety and effectiveness? Obviously effectiveness is evaluated as some sort of secondary category. Is that justified by the whole history of the act?

Mr. HUTT. I think from the beginning, back to 1906, Congress has understood that when an agency—and ours in particular—is faced, as the chairman pointed out earlier, between issues which affect the pocketbook as opposed to affecting life and health, one always puts the latter first on a priority basis. That does not mean we can ignore the former, and we do not ignore the former. However, it is taken into account in form of priorities.

Mr. DRINAN. Do I take it that if you had sufficient personnel and if the Congress were persuaded they should give an appropriation for this, effectiveness would be examined at the same level as safety?

Mr. HUTT. That is a fair statement, yes.

Mr. DRINAN. Has the Commissioner suggested this lately to the Congress? As an oversight committee we should say we would want to elevate effectiveness to the level of safety so the public is not paying out millions of dollar every year for drugs which are worthless.

Mr. HUTT. Father Drinan, if we had additional money at this time there are still issues of safety which we have not reached. If you are talking about the need for resources in the Food and Drug Administration we would be delighted if this committee would exercise oversight on that.

I can say that because I have only 1 week left with the Government and the Office of Management and Budget has less control over me than over others. Lack of resources is the major problem affecting the Food and Drug Administration.

When the General Accounting Office issues reports on our agency it issues reports asking us to do things which we do not have the resources to do. It is time that Congress and the public understood that.

Mr. FOUNTAIN. Before you do leave——

Mr. HUTT. I may leave a week earlier after that.

Mr. FOUNTAIN. I would appreciate it if you would submit for the record, for whatever it is worth, your opinion as to what you feel are the manpower needs of the agency and where the inadequacies may be.

Mr. HUTT. I do not have the time, much less the competence, to survey the entire agency even if I had 5 months as opposed to 5 days.

Mr. FOUNTAIN. In any given area, if you have any opinions. I do not want to burden you. I realize you are in the process of going elsewhere and do not want to take on extra burdens where you are. You perhaps would like them lessened.

Mr. HUTT. If you wish to hold 5 days of hearings, let's say a day for each bureau, to discover what it is that that bureau is not able to do because of a lack of manpower and money, those probably can be the 5 most important days of hearings this committee ever has held.

Mr. FOUNTAIN. One of these days I am hopeful we can do just that and find out what it is not doing which it could do and what its inadequacies are, and any other information we may get with respect to the way in which it is administering its responsibilities.

But we have so many agencies to oversee, it is difficult to find the time. However, I am hopeful we can do just that. I think you are right.

Mr. HUTT. From my personal standpoint, every day I see decisions made where we cannot do things because we do not have people to do them because other things have higher priority.

The public and the Congress do not adequately appreciate that. When you people sitting here ask us to do things you do not tell us what we should stop doing so we can do the other things.

Dr. GOLDBERG. Can you tell us quickly how many additional lawyers the General Counsel's Office requires?

Mr. HUTT. I can tell you how that has progressed, Dr. Goldberg.

When I arrived in September of 1971 we had 18 lawyers. At that time we were grossly understaffed.

Today we have 30, and by the fall we will have 38.

We are asking Congress for an additional 10 positions, 7 of which would be attorneys and 3 secretarial, to bring it to 45 attorneys.

A zero budget for my office prepared by FDA would put an adequate number at somewhere in the sixties or seventies.

Dr. GOLDBERG. That is your opinion of what the needs of the office are?

Mr. HUTT. Yes. I have long believed, Mr. Goldhammer, there should be an attorney in each of our regional offices to assist the compliance personnel out there. We have one now in Los Angeles, after a 3-year hiatus, who is performing very effectively in that capacity. We had one there for 20 years and for 3 years we did not have adequate personnel to put one there.

To give you historical perspective, in 1950 we had 20 lawyers. When I came in 1971 we had 18.

Mr. FOUNTAIN. Placing an attorney in the regional office makes sense to me, at least for the moment.

I realize you plan to allow exceptions to your monograph procedures and where a product is dangerous to health or constitutes rampant fraud FDA intends to take separate action against that product.

As I understand it, hexachlorophene OTC products, have been proceeded against, but I believe that that action occurred in January of 1972 just about the time the monograph regulations were first published as proposals. Is that true?

Mr. HUTT. That is correct. I believe it was the same day.

Mr. FOUNTAIN. Did you act in that case because of the reports that hexachlorophene was responsible for the death of infants in France?

Mr. HUTT. That was part of it but there were other pieces of information, also, Mr. Chairman. I believe all of the basis for that was laid out in the preamble and placed on file in the hearing clerk's office at that time.

Mr. FOUNTAIN. Mr. Goldhammer was reminding me that I made a statement on the floor of the House expressing my concern about this delay long before these deaths occurred. That is true.

After giving this information to the antiperspirant panel, as shown at page 2-76 of the verbatim transcript now in the hearing record, you said:

> But you can't let the exceptions overtake your rule. Or you would be back where I was in September 1971. The fact that the laxative panel has come up with half of its products being unsafe or uneffective doesn't remotely surprise me. I expect that will be true as we go through everything over a period of time.

Did I quote you correctly?

Mr. HUTT. Yes. I think 50 percent not making it into class III or class I would be a rough estimate.

Mr. FOUNTAIN. That does not——

Mr. HUTT. That does not mean they are unsafe.

Mr. FOUNTAIN. Continuing the quote:

> That doesn't mean that today, I should go out with that proposed regulation and take all those half of the products off the market.
> To do that would put me right back where I can't afford to be.

Now——

Mr. HUTT. That is correct.

Mr. FOUNTAIN. It appears you have spoken in general terms when you stated that half of the OTC laxatives on the market were found

to be unsafe or ineffective. Are you able to give us information as to how many were actually found to be unsafe? Do you have those?

Mr. HUTT. Unsafe? I was speaking in general terms in an informal session and used the figure half.

We would have to supply that information for the record. I am not entirely certain what those figures are.

Mr. FOUNTAIN. In your talk to the panel you used the word "unsafe" as applied to the laxatives.

Mr. HUTT. Unsafe in the sense that what I was referring to is that they were category II or III products and not category I.

Mr. FOUNTAIN. I imagine that means they are harmful and constitute a danger.

Mr. HUTT. That is exactly what it does not mean. It does not mean either of those. What it means is that there is not sufficient evidence. On a benefit-risk ratio the panel says there is no reason for them to be on the market. They go off the market pending future testing. That does not mean that one person ever has been harmed.

Dr. SCHMIDT. There is a way of thinking about this which helps a little bit because in many of our conversations with people I have noticed they have had a hard time with category II and saying, "Things are put in category II, and if so they must be unsafe."

What we are looking for is scientific and substantial evidence of safety and efficacy.

If that does not exist then things may be in category III or in category II, but it does not mean necessarily that there is positive evidence of ineffectiveness or some hazard.

We are looking for evidence of safety, evidence of efficacy. In the absence of that, things cannot be category I. They must be III or II.

Then a judgment is rendered as to whether or not experimentation could be done within a reasonable period of time; that such studies could prove the thesis that they are safe and effective and that proof can in fact be gathered. It is easier to understand category II and category III when approached that way than from the other way.

Mr. FOUNTAIN. I assume that whether something is safe or unsafe depends upon the context in which it is used. With all the things going on in the world today when we use the word "unsafe" I would think it is harmful.

Mr. HUTT. Mr. Chairman, again I was speaking at a closed session and using shorthand terminology which we use with the panels, people who have been working in this area for, say, a year, and who use the same shorthand I do.

Mr. FOUNTAIN. They knew what you meant?

Mr. HUTT. In my judgment, yes, because we had discussed this before.

Mr. FOUNTAIN. You had no particular reason for using the word "unsafe"—it was just part of the conversation?

Mr. HUTT. If I were to make a public presentation about it I would refer in a good deal more detail to the correct definition of those terms.

Mr. FOUNTAIN. Did the laxative panel find, in fact, that many of the laxatives on the market were unsafe?

Mr. HUTT. Actually harmful?

Mr. FOUNTAIN. Yes.

Dr. SCHMIDT. It might be helpful to have in the record the statements that we made at the time of the publication of the proposed

monograph, the report to me. We did speak to that issue. We were talking again about ingredients.

Mr. FOUNTAIN. That is right.

Dr. SCHMIDT. Some ingredients certainly were not well documented in the literature with regard to their safety and efficacy.

As I said then, and would say again, and we have said it many times this morning—were there evidence of a health hazard we would proceed immediately against that product.

Mr. HUTT. Mr. Pinco has reminded me that there were two which the panel found unsafe but not to the extent of being an imminent hazard to health.

The panel did raise some safety questions, as was true with the antacid report. Those products were reformulated even before the report reached the Federal Register. That is how quickly we are obtaining compliance, particularly where there is any real significant safety issue involved.

Mr. FOUNTAIN. Of course, any ingredient in a drug can make it unsafe. If you found two of these laxatives which were unsafe what is the justification for leaving them on the market?

Mr. HUTT. They were not.

Dr. SCHMIDT. They were not.

Mr. HUTT. They are off. What we are finding is that manufacturers have no future in putting out unsafe products any more than we as consumers have a future in consuming them.

When they find that the panels are concerned not just in a sense with a lack of evidence but with affirmative evidence of possible or potential harm, they are reformulating even before we can move the mechanism to require it.

[Note.—One of the laxative ingredients found by the advisory panel to be unsafe is podophyllum (podophyllin). In reply to a letter from the subcommittee chairman, FDA stated that as of July 3, 1975 podophyllin has not been removed from the marketed laxative. For further discussion of podophyllin and the exchange of correspondence, see pp.113–118 of this hearing record.]

Mr. FOUNTAIN. There would be no justification for leaving such products on the market under those circumstances?

Mr. HUTT. Well——

Dr. SCHMIDT. If there is evidence of an imminent health hazard then we will move immediately.

Mr. FOUNTAIN. Imminent?

Mr. HUTT. And also if there is evidence less than that, where the panel recommends that there is a sufficient potential health hazard that action should be taken immediately. We did it with TBS and with hexachlorophene, and we are now in the process of determining whether the same justification exists in the present circumstances for zirconium, which, as we all know, we cannot discuss today because it is a pending issue.

Dr. GOLDBERG. What is your position where the product has been found by the panel not to be generally recognized as safe? What do you do in that case in terms of permitting continued marketing?

Mr. HUTT. Dr. Goldberg, I find it difficult to know at what stage of the proceeding you are talking about and in which category.

Dr. GOLDBERG. Let's say the product has not voluntarily been taken off the market by the manufacturer prior to the publication of the final

monograph. If there is a question as to its safety, if this has not been established, what is your policy regarding leaving the product on the market?

Mr. HUTT. It is in category II or III?

Dr. GOLDBERG. Category II.

Mr. HUTT. In category II on the effective date of the monograph it goes off the market. That is spelled out in the procedure, and we spell out that, if at that point they do not comply, there is no question we will litigate across the board on that. However, it will be a different form of litigation from the old case-by-case approach. Here we have the rulemaking proceeding in place. We can ask for summary judgment in every instance, in my judgment.

Mr. DRINAN. Related to this, how does the procedure you outline affect Gillette's intention, as announced on March 24, 1975, to market a new zirconium aerosol on the basis that the monograph will not be completely finalized until next year or the year after? Will an NDA be required or will they be able to move forward?

Mr. HUTT. That issue is pending before the Commissioner, Father Drinan, right now.

The panel has recommended, as of 9 days ago, that we expedite action on zirconium and that all present zirconium-containing aerosol antiperspirants, the ZCAA's, should be acted upon immediately.

The Bureau of Drugs has that 100-plus page report which was made public the day after we received it. If you do not have a copy we would be happy to give it to you.

It is a very lengthy report. The Bureau of Drugs has that report. It will make its recommendations to the Commissioner within a matter of days. He will then act upon it.

Mr. DRINAN. In the interim can Gillette market its product?

Mr. HUTT. We are talking about only a week. Could they? We have no legal authority to prevent anyone from marketing any product.

If you are asking whether we will take legal action to prevent them, I think we would first, since it is only a week or two, wait to rule on this report.

Mr. DRINAN. Dr. Schmidt asked for an example of where FDA's monograph procedure has actually led to a new product being marketed. Perhaps this is such a case where Gillette has come forward and said: "We are, despite or because of the delay of the monograph procedure, we are moving forward to market a new zirconium aerosol."

Dr. SCHMIDT. The letter they wrote was prior to the panel's recommending that it be taken out of order. Gillette, in part by means of that letter, got resolution of a question they had. This was: "Are you going to take zirconium out of order or are you going to take it in 2 years?"

As you well know, if Gillette goes on the market with something, their investment in marketing and advertising could be in the tens of millions of dollars. I would judge they probably would not come on the market with anything once they learn that the panel was recommending that it be considered out of order. They would surely await my decision.

Mr. DRINAN. What is the fact of the matter? They announced their intention on March 24, 1975, 2 months ago. Have they in fact——

Dr. SCHMIDT. They have not.

Mr. DRINAN. All right.

Mr. FOUNTAIN. I get the impression that your current policy of deferring action against violative OTC products would encourage industry to take advantage of the moratorium. Apparently you do, too, Mr. Hutt. You told the antiperspirant panel:

> The people out in the industry aren't stupid. They see what we have done. And they see in some instances where they can take advantage of it. There is a new toothpaste called AIM. You have seen television advertisements. Until the OTC review, we had required an NDA for every fluoride toothpaste. Having adopted the policy of not litigating except in health or fraud issues, pending the OTC review, that particular company, and I don't remember which one it is, decided this was a good time to put out their new toothpaste without getting an NDA.
>
> Their competitors came in complaining. And said, "Damn it. We had to get an NDA. How come they don't have to get an NDA?"
>
> And we said it is really a matter of priorities and resources in FDA.
>
> If I were to start litigating against every AIM type product, then I would have my 18 lawyers spread all over the courts of the country again on a piecemeal ad hoc case by case basis instead of handling it on a comprehensive basis in this room.

Then you said:

> There have been probably 20 or 30 products of that type I can think of off the top of my head put on the market in the last year or two, taking advantage of that situation. And there, it puts me in a tough spot because I was the one who sort of made the principal decision 2½ or 3 years ago that this was the intelligent way to go.

Mr. HUTT. That is correct.

Mr. FOUNTAIN. In what appears to be your stated intent, to ignore the interstate marketing of new drugs without NDA's in conformance with the purpose——

Mr. HUTT. Mr. Chairman, I would point out one thing. When complaints were made about that particular toothpaste we went to the Bureau of Drugs, Mr. Yingling and I, and asked the Bureau whether there was any reason, from a health and safety standpoint or any other standpoint that they could determine, why this drug should be proceeded against for failure to have an NDA. The best judgment of the Bureau was that there was no possible serious or potentially serious issue which should be litigated.

Dr. GOLDBERG. Did the Bureau examine the formulation of the drug?

Mr. HUTT. They examined information, Dr. Goldberg. I could not tell you all that they did or did not examine.

Dr. GOLDBERG. I think there is a very salient question as to whether they had information on that particular product, as differentiated from other fluoride toothpastes; or whether they gave you an off-the-top-of-their-head opinion that it is like other flouride toothpastes and, therefore, they saw no particular safety issue.

Mr. HUTT. My best judgment is that they did have information about it and they concluded there would be no difficulty today in anyone making a safe and effective flouride toothpaste.

Dr. GOLDBERG. Do you know for a fact they had information on this product?

Mr. HUTT. I know they had information. You asked me which information they had. I do not know.

Mr. FOUNTAIN. Do you know whether or not they had information as to whether or not the company had adequate controls?

Mr. HUTT. Adequate controls?

Mr. FOUNTAIN. Yes; manufacturing controls.

Mr. HUTT. Our best judgment today is that the way to review adequate manufacturing is to go to the plant and not to require an NDA. If the only issue is whether a manufacturer has adequate manufacturing procedures then we should determine that by sending an inspector to the plant to review the manufacturing procedures, not by requiring a new drug application which deals with basic safety and effectiveness.

Dr. GOLDBERG. You always did that. That is nothing new.

Mr. HUTT. That is true. That is exactly true.

Dr. GOLDBERG. That is part of the NDA approval process.

Mr. HUTT. That is part of it but that is not the reason for the NDA. The reason for the NDA is to establish safety and effectiveness, and unless there is some kind of special manufacturing problem, which crops up every once in a while with a drug where a manufacturing procedure is critical in terms of safety or effectiveness, the NDA should not be used properly as a means of surveillance over manufacturing.

Dr. GOLDBERG. Might we request the witness to make a submission for the record identifying the kind of clinical, animal and other data that were available to the Bureau of Drugs with respect to "Aim" at the time they gave you that opinion?

Mr. HUTT. Surely.

[The information referred to may be found in the appendix at p. 317.]

Mr. DRINAN. Is it fair to say that 3 or 4 years ago, when zirconium and all these products applied for an NDA, or should have applied, is it fair to say in light of the recommendation by the advisory committee that the FDA should have denied access to the market at that time? I quote the bottom line—

> Because conclusive testing to establish the safety of zirconium-containing aerosol antiperspirant might take years to accomplish, and because in that time millions of consumers would be unnecessarily subjected to risk we recommend that this be withheld from interstate commerce.

Is it fair to say now in retrospect that the FDA should have at the initial stage denied access to the market?

Dr. SCHMIDT. This is the conclusion that comes after months of study, testimony by world experts in a brand new, relatively speaking, field of medicine. Just in the past few years the relationships to immunity to pulmonary granulomas have been studied extensively, so that kind of conclusion can be drawn only after a process like this panel went through. Therefore my answer would be no. It would have been arbitrary in 1972.

Mr. DRINAN. You mean the information just was not there. Nobody really had a clue that this particular danger might be in this particular drug called zirconium?

Dr. SCHMIDT. I think probably the key data that raised this question were supplied by Gillette which reported lesions in monkeys from inhalation of their product. This was subsequent to 1972.

Mr. HUTT. As contrasted, Father Drinan, with the Procter & Gamble studies which showed no problem.

Mr. FOUNTAIN. Was this done before the drug was marketed?

Mr. HUTT. The Procter & Gamble studies were done and showed no problem.

Dr. GOLDBERG. You know that only in retrospect. You do not know, Mr. Hutt, whether your Bureau of Drugs people would have accepted those studies as adequate at the time.

Mr. HUTT. In hindsight one does not know whether they would have accepted them or not.

Dr. GOLDBERG. That is what the new drug approval process is all about. We don't know.

Dr. SCHMIDT. Because of some evidence that has come up we are talking about one thing and one type of spritzer can. There are many, many kinds of spritzer cans with many, many kinds of products in them. We are concerned about all of them and we are reviewing all of them.

Dr. GOLDBERG. That is fine and I have no objection to that. However, we are discussing not only whether it is good policy, but also whether the law requires that new drugs be examined for these considerations before they go on the market, rather than in hindsight.

Dr. SCHMIDT. Perhaps I was not explicit in relating the OTC drug review process to what we did in 1972 with regard to zirconium-containing antiperspirants.

Mr. DRINAN. What about the person who wants to merchandise a product? He obviously has the burden of proof. If he wants to be on the GRAS list he has the burden. Was an original NDA application——

Mr. HUTT. That is not true, unfortunately, under the law.

Mr. DRINAN. The burden?

Mr. HUTT. The burden is on us to prove a product is a new drug.

Mr. DRINAN. It was decided this was not, I take it?

Mr. HUTT. That is correct. It was decided it was a newly marketed old drug.

Mr. DRINAN. Was that an error?

Mr. HUTT. In my judgment, no, not at that time. Today it would be; yes.

Mr. DRINAN. You didn't even get to the question of the safety. You just said this does not really need an NDA because it is an old drug.

Mr. HUTT. It was decided that the marketing at that time should not be objected to by the Food and Drug Administration. We had no reason to believe there was a problem with it. We therefore did not object to the marketing and said that the product, like hundreds of other OTC drugs coming on the market every day, would be reviewed by the OTC drug review.

Mr. DRINAN. You say there was no reason to question the safety. Is that really true, that in all of the literature and all the science available none of the information that has now come out was available?

Mr. HUTT. That is not true.

Mr. DRINAN. You are contradicting yourself.

Mr. HUTT. I am sorry, sir.

Mr. DRINAN. You said there was no reason to question the safety.

Mr. HUTT. In retrospect today, just as one could do it with every OTC drug on the market today, one can raise questions, but in terms of making a decision as to whether there was any greater reason to doubt the safety of that than 200 or 400 or 200,000 other products on the market, there was at that time nothing that we were aware of or we would not have made that decision.

One can say——

Mr. DRINAN. Should you have been aware of it?

Mr. HUTT. One can ask that question as we go through individual drug by drug, every drug on the market today. Questions will be raised about safety, about effectiveness, about proper labeling.

We testified when we were last here that every single OTC drug on the market today, all 200,000, will be required to be either reformulated or relabeled or both.

Now, one can say, therefore, that from 1906 to the present, FDA has not been doing its job if one wants to look in hindsight and say with all of today's knowledge we know everyone was wrong in the past.

I point out to everybody that the same thing will be said 20 years from now. Products that this panel has reviewed and said are safe and effective will in 20 years be questioned on the basis of new information and a new insight into that information and someone will say the earlier panel was wrong.

Mr. DRINAN. I agree with that. What I am asking is whether the information here is so new that at the time the FDA gave clearance to these drugs some years ago they legally could not have foreseen and are to be blamed for not foreseeing what we now know?

Mr. HUTT. My answer would be yes; but that is a matter of judgment, solely a matter of judgment.

Mr. FOUNTAIN. Other than what you have said today, do you have evidence, documented evidence, evidence in your records, that this was not a new drug?

Mr. HUTT. Documented record evidence? I am not sure——

Mr. FOUNTAIN. Was it found by FDA not to be a new drug?

Mr. HUTT. I am not sure what documented record evidence would mean.

Mr. FOUNTAIN. Anything other than what you have said.

Mr. HUTT. A file memorandum where it says this?

Mr. FOUNTAIN. Yes.

Mr. HUTT. We do not have that. To the best of my knowledge we do not have that for 99.99 percent of the OTC drugs on the market today.

Mr. FOUNTAIN. Notwithstanding the request——

Mr. HUTT. I am talking about products which went out 20 or 30 years ago.

Mr. FOUNTAIN. I am talking about new applications.

Mr. HUTT. If I want to go out when I leave the Food and Drug Administration and start a pharmaceutical company and market aspirin, the Food and Drug Administration does not require me, nor should it, nor legally could it, to obtain an opinion and document that it is an old drug.

Dr. GOLDBERG. What if a manufacturer came forward and said, "We are going to market aspirin in aerosol form." How would you feel about that?

Mr. HUTT. Today?

Dr. GOLDBERG. Yes.

Mr. HUTT. I doubt we would approve it today.

Dr. GOLDBERG. Why do you assume you would have made that decision with respect to the zirconium aerosol? There is no evidence——

Mr. HUTT. I am not sure I understand the relevance of the question. You are asking about apples and oranges here.

A decision was made in 1972. You are now saying, on the basis of hindsight, and I realize hindsight is much better, that if I knew in 1972 about zirconium what I know today obviously that decision would not have been made.

That is true throughout all of history.

Going back, FDA over the years has given thousands of written opinions, which we subsequently revoked in 1968, but literally thousands of written opinions that various drugs, prescription and OTC, were old drugs; that is, no longer new drugs, and thus not required to have NDA's.

I think Mr. Goldhammer and I would agree in hindsight that was a bad mistake back when that was done.

Dr. GOLDBERG. I like your macroscopic treatment of the drug world. But getting back to the point I raised, and which you have not dealt with, is the matter of whether you can say today what FDA would have done in 1972 if, in fact, it had processed the abbreviated new drug application submitted by Procter & Gamble.

You retained the data filed by the company, but there is no evidence that it was reviewed by FDA. And there is no evidence, and there couldn't be such evidence since it was not reviewed, as to whether or not questions would have been raised about the kinds of studies done, the adequacy of the preclinical and clinical data, and so forth, if the application had been reviewed. It may simply have been deferred, like many other drug applications are.

In connection with the status of the drug in 1972, as far as we are aware, there is no documentation in the files of FDA that anyone in the agency made the decision that this was not a new drug, and you did not communicate that to the manufacturer.

Mr. HUTT. It was not necessary to and I do not believe they asked for an opinion on that. They submitted an abbreviated NDA.

Dr. GOLDBERG. Your explanation to them——

Mr. HUTT. Was that it would be deferred pending OTC drug review.

Dr. GOLDBERG. You would not look at the evidence at the time it was submitted.

Mr. HUTT. If we had concluded that it was a new drug, it would have been illegal to put it on the market.

Mr. FOUNTAIN. Let me read the letter of June 20 from the Food and Drug Administration signed by Dr. Bryan, Bureau of Drugs.

Mr. DRINAN. When is that?

Mr. FOUNTAIN. June 20, 1972, addressed to Procter & Gamble, attention Mr. T. W. Mooney.

Gentlemen:

Reference is made to your abbreviated new drug application dated January 10, 1972, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Secret (aluminum hydroxychloride, zirconyl hydroxychloride and hexachlorophene) antiperspirant.

Pursuant to the policy of review of over-the-counter drugs as stated in the Federal Register announcement of April 20, 1972, the material you have submitted will not be reviewed at this time but will be handled by the appropriate OTC panel at a later date.

The material you have submitted will be retained in our files.

Mr. HUTT. Yes.

Mr. FOUNTAIN. What does that letter mean?

Mr. HUTT. It means we have no reason not to permit it to be marketed at this time; that is until the OTC drug review determines different, it is not a new drug and does not require an NDA before it is why being marketed.

Mr. DRINAN. If Procter & Gamble thought it was not a new drug, why did they submit it? They must have thought so.

Mr. HUTT. Undoubtedly. We concluded it was not necessary, which I must say is a process that FDA has used going back to 1938.

Mr. DRINAN. Maybe they have been making mistakes since 1938?

Mr. HUTT. That is possible.

Mr. DRINAN. In this case, is there further evidence besides the letter of June 20, 1972, as to who examined it, under what conditions, and how can you justify this as coming within the intent of the law? You categorically say it is not a new drug. You do not even get to the question of safety

Procter & Gamble, with their lawyers and chemists, thought it was a new drug, and they applied. Therefore the burden is on the Commission to say you have concluded, contrary to their evidence, this is not a new drug.

Mr. HUTT. Again if we had any reason to suspect, whoever reviewed it in the Bureau of Drugs, Dr. Paul Bryan, who wrote the letter and who was at that time the Director of the drug efficacy study implementation project, would have made a different decision. It was sent to him because there had been published in the Federal Register a notice stating the conclusion of the National Academy of Sciences, and FDA's concurrence, that zirconium in nonaerosol form was effective, and they were submitting an abbreviated application for the aerosol version of that product.

We concluded there was no purpose to be served by having an abbreviated NDA at that time.

If we had pursued this without the OTC review, of course we would then have processed it.

However, we had the OTC drug review in place precisely to handle these issues and saw no reason to keep the product off the market, any more than Aim toothpaste, pending the OTC drug review.

Mr. DRINAN. What had the National Academy said precisely against it?

Mr. HUTT. They had said zirconium in antiperspirants, which are in cream and roll-on forms, is effective.

Mr. DRINAN. Procter & Gamble was marketing an aerosol.

Mr. HUTT. That is correct.

Mr. DRINAN. You had no scientific finding on that?

Mr. HUTT. But at that time we did not have knowledge of what we now realize is a problem. We did not have an understanding, which comes over a period of time as new information develops——

Mr. DRINAN. Dr. Bryan, apparently all on his own, said, "I don't think the additive here or the new circumstance that this is in aerosol

form makes any difference," even though the National Academy of Sciences said nothing about that precise question.

Mr. HUTT. That is a conclusion you have drawn, that he did it all by himself.

Mr. DRINAN. Tell us about the process.

Mr. HUTT. One of the problems today is that we did not realize this was going to be an issue at this hearing. If the committee had informed us they wanted us to look into who Dr. Bryan talked to, we would have done so. We can do that.

Dr. CROUT. If there were no OTC drug review in place, quite obviously that ANDA would have been reviewed and a determination would have been made, and the problem would have been handled earlier than it is being handled now.

However, we would have ended up with no determination about the products of other firms and we would have ended up with no class determination about aerosols in general.

Once the OTC drug review was in place, we made a determination to put all OTC drug products into that review unless somebody has positive evidence there may be a safety hazard so we should take it out of turn.

There is a new piece of information not available at that time that I would like to emphasize, and that is that zirconium-containing aerosol antiperspirants may be different from aluminum-containing antiperspirants. That is a possibility.

I think it was quite reasonable at that time, for whoever reviewed that, to consider the zirconium-containing aerosol as just another aerosolized antiperspirant. They had been on the market a good number of years.

Therefore, the separation of zirconium-containing from aluminum-containing antiperspirants as a possible health hazard occurred as a result of the panel's work.

I don't think one can now go back and ask whether we would have made a different decision in 1972 if we knew then what we know today. The answer is obviously "Yes."

Mr. DRINAN. No matter how you put it, it seems to reflect badly on FDA. The FDA did determine in 1972 that zirconium aerosols were not new drugs. You had to reach that conclusion.

Dr. CROUT. We did not make that a positive determination.

Mr. HUTT. It was the inherent determination, no question.

Mr. DRINAN. On what basis did FDA make that decision where zirconium aerosols were on the GRAS list?

Dr. CROUT. The decision was not made in those terms.

Mr. DRINAN. The decision was made. Dr. Bryan's letter says "go right ahead. You don't need an application."

Mr. HUTT. It may have been on the market before then, incidentally.

Dr. CROUT. It was.

Mr. DRINAN. I want to know. Zirconium aerosol was on the market?

Dr. CROUT. Yes.

Mr. DRINAN. How did it get there without FDA approval?

Dr. CROUT. Because, as we pointed out, for years and years OTC drug products have been appearing on the market without prior Food and Drug Administration review.

Mr. DRINAN. But that does not prove anything. It could have been out there because of a bootlegger.

Dr. CROUT. We are not saying what it proves. But a general assumption of the OTC drug review is that when we make a decision on whether a drug is in the review or not, the general assumption is that the drug is in unless it has a safety problem. That is an inherent determination of old drug status.

Mr. DRINAN. You are telling me zirconium aerosol was not a new drug, and that is what you told Procter & Gamble on June 20, 1972. I am asking as a simple country lawyer, tell us more about how zirconium aerosol could have been an old drug everybody knew about.

Mr. HUTT. We seem to go around in circles on this. All we can say is what has happened in the last 100 years on OTC drugs. Before there was a 1906 act, between 1906 and 1938, between 1938 and 1962, and up to the present, virtually all OTC drugs have been marketed by the industry without coming in and getting Food and Drug Administration approval. The law permits them to do that. The statute does not require them to obtain an opinion from FDA even if we say it is a new drug. The statute says we are then required to go out and take regulatory action to get that product off the market.

There is absolutely nothing which requires them to ask our opinion.

Procter & Gamble first marketed its product in August 1971. That was a year before they came in, or roughly a year before they came in, with their abbreviated new drug application.

They went into national market in August 1971, so they probably first marketed this in test marketing perhaps even as much as a year earlier, without an abbreviated new drug application.

My colleagues have reminded me that probably the reason they came in with the abbreviated new drug application was because of the hexachlorophene in the product, not because of the zirconium.

You catch us a little off guard here in a sense. We are trying to reconstruct off the tops of our heads events of 3 years ago which involve people whom we did not bring with us.

Mr. DRINAN. This is directly and essentially relevant to what we are talking about in these hearings, the role of the advisory committee.

Mr. HUTT. I do not understand that.

Mr. DRINAN. You told Procter & Gamble: "The advisory committee will take this, Procter & Gamble, you have no worry. You don't need an application."

In contradiction to your statutory responsibilities, you turned this over to the advisory committee.

Mr. HUTT. I am sorry, I cannot agree with you. The company marketed its product without any kind of an NDA. If it were not for this advisory committee this problem never would have been caught. The reason they submitted their abbreviated NDA, apparently now, may not have been zirconium at all but hexachlorophene. Once they got rid of hexachlorophene they could have gone back and marketed zirconium. There would have been no abbreviated new drug application, no panel, no discussion of the issues in this 100-page report, and the public would not be protected.

It is because of the OTC drug review that we are catching up with this product and doing it right.

Mr. DRINAN. I agree, but I wonder why you did not say in the beginning that until or unless the FDA gives clearance you are not allowed to put it on the market.

Let me ask a simple question: Did Procter & Gamble, in its application, seek to justify the safety aspects of their product at all?

Mr. HUTT. We will have to go back and look at the new drug application. We do not have it with us. We simply did not review it in preparation for today.

Mr. FOUNTAIN. I have to rely to a large extent on the information I get from the staff, and the material we read, as well as the regulations which have been read and which we have had an opportunity to observe.

However, as I understand it, I thought you were required to make a review of any application which included hexachlorophene. Is that not right?

Mr. HUTT. Mr. Fountain, what I would think might be the best way to handle this is for us to go back, since we were not told this whole abbreviated NDA would be the subject of detailed discussion, and see exactly what was in that NDA, what the status was, why it was submitted, and make a full report to you.

Mr. FOUNTAIN. All right, and also include in that report an explanation as to why, after Gillette submitted information indicating that the inhalation of zirconium in the lungs of animals in October of 1973 was harmful——

Mr. HUTT. It showed a harmful result for the Gillette product and not for the Procter & Gamble product.

Mr. FOUNTAIN. But Procter & Gamble had zirconium, did they not?

Mr. HUTT. Yes; but it showed an effect for one product and not an effect for another product.

Mr. FOUNTAIN. The point I make is not that they were identical, but after you had this information back in October of 1973, and you had had this abbreviated new drug application, where you sort of said you will not pay attention to it now—put it in the file—why you did not go back and take a look at this situation.

Dr. CROUT. We did. The slides from the Gillette study were reviewed by one of our toxicologists, as were the data in both studies. It was his judgment that the data did not provide any evidence that the Procter & Gamble product was unsafe, so that actually it turns out——

Mr. FOUNTAIN. Procter & Gamble, but what about Gillette?

Dr. CROUT. Gillette's was not marketed.

Mr. HUTT. Their product was withdrawn from the market.

[The information requested may be found in the appendix at pp. 331–333.]

Dr. CROUT. Let me make one final comment. Interestingly enough the panel here is being more cautious, more severe, more stringent than our own internal review. I merely want to point out that reasonable men can differ, and in the long run the panels may come up with positions which are quite as strong as any position we might take internally, sometimes even stronger.

Mr. HUTT. Also, Mr. Chairman, there is a difference between what the panel is focusing on and what the internal review focused on.

The panel is, I think, not disagreeing with the analysis of the Bureau of Drugs, but it is looking at potential long-range possibilities which the public should be protected against.

Dr. CROUT. The purpose of our review, again, was to ask basically whether there is a safety problem sufficient for us to take the Procter &

Gamble product out of the OTC drug review. A judgment was made there was not reason to do that.

Dr. GOLDBERG. You were looking at that question in a very narrow context which you describe?

Dr. CROUT. That is correct.

Dr. GOLDBERG. However, am I not correct in saying that the NDA process, as it has traditionally been viewed by FDA, is to take the broad view; to examine not only whether there is evidence of potential danger to individuals today, but also whether there are questions of safety for the future. Isn't the panel, in effect, doing what FDA should be doing in the new drug process?

Dr. CROUT. Of course, but the panel is taking that broad approach, and we know it.

Dr. GOLDBERG. Which is FDA's normal approach.

Dr. CROUT. The panel works for FDA. Of course it is our approach. That is right. We are careful in instructing those panels, and so on. You bet that is their approach.

Dr. GOLDBERG. I want the record to show that the panel is not doing something over and above FDA's normal in-house responsibility. It is not that they are applying more stringent standards; they are doing the kind of thorough job that FDA has often done in the past and should be doing regularly in examining these products.

Dr. CROUT. Fair enough.

Mr. FOUNTAIN. If you come to the conclusion that certain decisions should be made, even though you turn it over to a panel, you do not have to wait for the panel to make a recommendation. Is that true?

Mr. HUTT. That is correct.

Mr. FOUNTAIN. I was reading some quotes from you in your conversation with the panel, Mr. Hutt. I was in the process of asking a question when we got involved with these other questions, all of which are important.

Is your stated intent, as I gather it from this colloquy here, to ignore the interstate marketing of new drugs without NDA's, in conformance with the purpose of the statute expressly prohibiting such marketing?

Mr. HUTT. First, that was not my stated intent. My stated intent was that the marketing of products which present no known safety or effectiveness issues, while the panel was in the process of reviewing products which fall into that class, was not something that we should put as a major enforcement priority, Mr. Fountain.

If those were determined by FDA clearly to be new drugs, then that would have been a different issue.

Mr. FOUNTAIN. We had hoped we would be able to cover more than we have today, and that we would be able to cover other areas, but I doubt we will be able to. We will have to pick a later time.

We shall adjourn until Monday morning.

Mr. DRINAN. Thank you very much, gentlemen. You are very good witnesses.

Mr. FOUNTAIN. We shall continue on Monday morning, at 9:30.

[Whereupon, at 12:30 p.m., the subcommittee adjourned, to reconvene at 9:30 a.m., Monday, May 12, 1975.]

USE OF ADVISORY COMMITTEES BY THE FOOD AND DRUG ADMINISTRATION
(Part 2)

MONDAY, MAY 12, 1975

HOUSE OF REPRESENTATIVES,
INTERGOVERNMENTAL RELATIONS
AND HUMAN RESOURCES SUBCOMMITTEE
OF THE COMMITTEE ON GOVERNMENT OPERATIONS,
Washington, D.C.

The subcommittee met, pursuant to notice, at 9:43 a.m., in room 2247, Rayburn House Office Building, Hon. L. H. Fountain (chairman of the subcommittee) presiding.

Present: Representatives L. H. Fountain, Don Fuqua, Edward Mezvinsky, Barbara Jordan, Robert F. Drinan, Glenn English, John W. Wydler, and Robert W. Kasten, Jr.

Also present: Delphis C. Goldberg, professional staff member; Gilbert S. Goldhammer, consultant; and Richard L. Thompson, minority professional staff, Committee on Government Operations.

Mr. FOUNTAIN. The subcommittee will come to order.

The record will show that a quorum is present.

Mr. Hutt, I have one or two clarifying questions based upon a telephone call received over the weekend.

We were informed by two sources, one of which was Mr. Goodrich, that months before you became Associate General Counsel for FDA in September 1971, Dr. Edwards and Mr. Goodrich decided to regulate OTC drugs on a class basis by rulemaking and had already testified to that effect before Senator Nelson's subcommittee.

In your testimony here on Friday, I am not sure what you intended, but in your statement to the antiperspirant panel on March 24, 1975, was it your intention to convey the idea that the rulemaking on a drug-class basis originated with you?

STATEMENT OF ALEXANDER M. SCHMIDT, M.D., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION; J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS; PETER BARTON HUTT, CHIEF COUNSEL; ROBERT C. WETHERELL, JR., DIRECTOR, OFFICE OF LEGISLATIVE SERVICES; ROBERT G. PINCO, CHIEF, DIVISION OF OTC EVALUATION; MARK NOVITCH, M.D., DEPUTY ASSOCIATE COMMISSIONER FOR MEDICAL AFFAIRS; AND GARY L. YINGLING, ASSOCIATE CHIEF COUNSEL FOR ENFORCEMENT

Mr. HUTT. No, sir. I said I believe I was one of the people who had to make the decisions, or something to that effect. I believe in that

statement I was referring specifically to the question of continuing after the rulemaking had begun with the case-by-case litigation.

Mr. FOUNTAIN. I might add that Mr. Goodrich informed the staff that FDA had never contemplated any deferral of enforcement of the new drug provisions of the act during the pendency of the panel review and the publishing of the final rules; that is when he was there.

Dr. Schmidt, the antiperspirant panel was composed primarily of experts in the field of dermatology. Is that right?

Dr. SCHMIDT. I would have to review the curriculum vitae of the panel members before I can characterize them. I am not sure that is correct.

Mr. FOUNTAIN. Were any of the panel members experts in lung pathology?

Dr. SCHMIDT. There was one person.

I make two points. One person was generally familiar, at least, with the field, but this panel consulted widely with some of the world's experts in the question areas they were taking up. Panels all have access to expertise all around the world.

This panel, in particular on the zirconium issue, consulted very widely.

Dr. Clayton, a toxicologist, and a microbiologist were on the panel; a pharmacologist, a pharmacist.

Dr. Rosenberg is a dermatologist who is listed. Another comes from a department of dermatology.

I would also remind you that dermatologists today, particularly academic dermatologists, have a wide variety of skills and get into molecular biology and the sorts of things that academicians do in many areas.

Mr. FOUNTAIN. As a matter of fact, a general practitioner of law has a general knowledge but I would hate to rely on him altogether when it comes to a specialty field.

Then I take it that no member of the panel was an expert in lung pathology except as you have described, but the panel was in a position to get information from all of the sources you mentioned.

Mr. PINCO. It depends on how you define the term "expert." I think several members had a working knowledge of this area. They also had enough knowledge to realize that there were areas they did not have all the expertise they needed. That was one of the reasons they went to various people from all over the world, to try to bring them together for that very purpose. That was the reason they had that meeting and subsequent meetings, to build on that knowledge which they had.

Mr. FOUNTAIN. Strike out the word "expert." Did you have a lung pathologist?

Mr. PINCO. Not as such.

Mr. HUTT. I believe at the hearing two times ago that we agreed to provide the curriculum vitae of the experts who were brought in by the panel and on whom they relied in these areas that you are now talking about, also.

Mr. FOUNTAIN. Then I take it from what you have said, Dr. Schmidt, that you regarded the panel, or you regard the members of the panel, as experts qualified by experience and training to evaluate the safety of inhalation of zirconium aerosols?

Dr. SCHMIDT. Certainly they are competent to conduct the review which they have conducted. I would emphasize that many people have volunteered to me information that this panel gathered together the true experts in zirconium and zirconium toxicity, and so on, from around the world. The panel had the best advice that science can offer, and they certainly are qualified to evaluate the scientific information that they receive.

Mr. FOUNTAIN. Then you say they were qualified to evaluate the safety of the inhalation of zirconium aerosols?

Dr. SCHMIDT. Yes.

Mr. FOUNTAIN. During the hearing on May 9, I placed into the record documents indicating that the Food and Drug Administration established a policy of withholding regulatory action against OTC and many prescription new drugs on the market without NDA's pending review by OTC review panels.

At this time I shall place into the record additional documents to further illustrate FDA's policy of deferring action until after OTC panel review.

The documents relate to "Podophyllum: A potentially dangerous laxative * * *."

[The documents referred to follow, as does an exchange of correspondence between the subcommittee chairman and FDA Commissioner Schmidt concerning podophyllum (podophyllin). See pp. 309–317, 333–337 of this hearing record for documents relating to advisory panel's finding that podophyllum is unsafe.]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

Date: June 18, 1971.
Attn of: BD–2.
Subject: Podophyllum: A potentially dangerous laxative, by G. Rosenstein, M.D. et. al.
To: Henry E. Simmons, M.D., M.P.H. (BD–1).

Podophyllum is an irritant substance used internally as a laxative (8 to 15 mg.) and topically for warts (20–25% Conc.). The authors have documented that podophyllum should no longer be used as a laxative. It is not dangerous to the patient in the doses in which it is present in proprietary laxatives, provided that an overdose is not taken, but there is a report of phocomelia in the offspring of a patient who took "herbal slimming tablets" containing podophyllum during the 5th to 9th week of pregnancy. Whether this is or is not drug-related is not known but phodophyllum does have an effect on mitosis, which renders it useful topically for the treatment of warts. In the past, it was used topically for various malignancies.

Topical podophyllum preparations taken orally by accident or with suicidal or abortifacient intent have caused death following doses of 300–600 mg., but some patients recovered following good supportive therapy. One patient is reported to have gone into coma 24 hours after application of podophyllum ointment in the treatment of condylomata acuminata.

The following documentation is offered for removing podophyllum from the list of accepted ingredients for OTC cathartics:

1. Following the report of phocomelia in the literature (Lancet) in 1962, the British manufacturer of the tablets in question withdrew them from the market and substituted another ingredient.

2. The Ministry of Health of Italy informed WHO in 1963 that podophyllum preparations should be labeled "Do not use in confirmed or suspected pregnancy".

3. Windsor Cutting's "Handbook of Pharmacology", 3rd Edition, states, under Vegetable Cathartics that podophyllum (and other examples) have no modern use as cathartics.

4. Goodman and Gilman lists podophyllum under the Obsolete Cathartics. They say that the obsolete cathartics "are described only because they represent a potential source of drug abuse and intoxication. Their use cannot be too emphatically condemned." With respect to the cathartic resins, in particular, including podophyllum, they state that they act on the small intestine, are quite irritating, and that several are still common ingredients in irrational cathartic mixtures. "The cathartic resins should be abandoned".

5. In pregnant mice, a dose of 4 mg./kg. podophyllotoxin I.V. caused interruption of pregnancy in 100% of cases. (Didcock, K. A. et al.: The Action of Podophyllotoxin on Pregnancy, J. Physiol. 117:65,1952.)

6. Repeated applications of 20% podophyllum to the mouse cervix revealed that it is a weak carcinogen. (Garret, M.: Relationship of Podophyllum to Carcinogenesis, Cancer 19:947, 1966.)

7. The Medical Letter, Dec. 21, 1962, issued a warning against podophyllum during pregancy following the report on phocomelia. It mentioned that podophyllum is present in Carter's Little Pills, and other cathartic mixtures.

Recommendations

1. The paper by Dr. Rosenstein, et al., makes a contribution and is recommended for ultimate publication in revised form. Since it comes from FDA personnel, however, it should not be published unless or until the Commissioner moves to withdraw podophyllum from laxative preps. by a S.P.I.

2. There is ample evidence that podophyllum is obsolete as a cathartic and a recommendation should go forward to the Commissioner along with a proposed S.P.I.

3. An attempt should be made to identify the currently marketed OTC and Rx podophyllum-containing products. A printout accompanying this paper reveals a number of old products under NDAs. Some "Cold Tablets" contain podophyllum in small quantities (1.5 mg./tab.); a number of laxative combos. containing podophyllum are also listed but how many of these are still on the market and what else is on the market remains to be ascertained.

4. When ultimately published, the thrust of the paper should indicate why oral podophyllum was removed from the market.

5. If you concur, I will arrange for S.P.I., and a briefing memo to Dr. Edwards, including a list of orally administered podophyllum-containing drugs. Carter's Little Pills are the best known, I suppose, but there is no reason why they cannot reformulate.

MARION J. FINKEL, M.D.,
Deputy Director,
Bureau of Drugs.

MEMO RECORD, APRIL 14, 1971; OFFICE: OSE; DIVISION: SHEDF

From: V. Berliner, pharmacology.
To: Dr. H. Ortiz through Dr. G. Rosenstein.
Subject: Podophyllum, re your request for Pharmacology opinion on hazards and actions.

SUMMARY

Goodman and Gilman state on p. 1029 of the Fourth Edition, 1970 of their "The Pharmacological Basis of Therapeutics: The cathartic resins should be abandoned". Podophyllum is in this group. It is a cytoxic agent that acts as a spindle poison thus interfering with mitotic processes. This property confers also an embryotoxic and teratogenic potential. It has to be admitted that in spite of the wide usage of this drug in several cathartic formulations the teratogenic property became demonstrated in only few instances but it is possible that minor expressions of this action went unnoticed and were not associated with podophyllum intake. This insidious behavior may make it even more undesirable for routine use as a cathartic.

There are no animal investigations that were conducted according to our present guidelines for teratogenicity studies. It would be of academical interest to find out how a drug with these properties would act in these studies and it might be a worthwhile undertaking for OPRT. However, these studies are not suggested as a basis for any action against Podophyllum. These could rest mainly on the already available knowledge, that was compiled by Dr. G. Rosenstein.

These considerations pertain only to the use of podophyllum in cathartics. It still may have merits for the treatment of conditions requiring cytotoxic functions.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Director, OTC Products Review Staff (BD–109).
Through: Acting Director, Bureau of Drugs (BD–1); Assistant to the Director for Regulatory Affairs (BD–30).

PODOPHYLLUM CONTAINING DRUGS

We have been requested to draft a policy statement which bans cathartic preparations containing podophyllum and restricts the drug to prescription sale for other drug uses. The policy statement is based on two reports of teratogenicity and one report of severe peripheral neuropathy with accompanying intrauterine death. No conclusions were made on any of these reports as to the relationship of the drug to the fetal incidents.

We have discussed the proposed policy statement with Dr. Philip Walters, of OSE, and he had advised that the status of the drug as a safe and effective cathartic should be considered by the OTC Panel reviewing this class of drugs before we take any official action on our own. Mr. John McElroy of your office informs us that the panel is actively reviewing at least one product containing podophyllum (Carter's Little Pills) and a review of the data submitted by the firm reveals that the enclosed articles which are the basis for the proposed SPI are not among those submitted by the firm. We are also enclosing the background material prepared by Dr. Gladys Rosenstein.

Since the background support for the SPI is not awesome, we recommend that the OTC panel thoroughly review the matter, including the two enclosed articles, and that the Bureau's final action be taken based on that review. The matter of safety and efficacy of the topical use of podophyllum and its derivates will be considered at that time.

Podophyllum, we are advised does not raise a safety issue that warrants its separation from the normal OTC Drug Review process.

MARY A. MCENIRY.

INTERGOVERNMENTAL RELATIONS AND
HUMAN RESOURCES SUBCOMMITTEE,
Washington, D.C., May 16, 1975.

Dr. ALEXANDER M. SCHMIDT,
Commissioner, Food and Drug Administration,
Parklawn Building,
Rockville, Md.

DEAR DR. SCHMIDT: During the testimony on May 9, 1975, you and Mr. Hutt indicated that two laxative ingredients were found to be unsafe and that the firms marketing the drugs reformulated the products even before the publication in the Federal Register of the proposed laxative monograph.

It is my understanding from the proposed laxative monograph published in the March 21, 1975 Federal Register that podophyllin was one of the two laxative ingredients which were found unsafe. I would appreciate knowing when Carter-Wallace removed podophyllin from its formulation, whether it has ceased shipping the podophyllin product, and whether any action has been taken to remove from the market the existing stocks of podophyllin-containing pills.

Sincerely,

L. H. FOUNTAIN, *Chairman.*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., July 3, 1975.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations and Human Resources, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: This replies to your letter of May 16, 1975 concerning the removal of podophyllin from the formulation of the drug, Carter's Little Pills.

Our belief that podophyllin was being removed from Carter's Little Pills was based on the firm's written communication of November 8, 1974 to the Over-the-Counter Laxative Panel to the effect that Carter was making plans to retain its pill form but would change its present formula to provide for the removal of podophyllin. That communication is attached.

In our followup on this matter we have learned that podophyllin has not yet been removed. The firm has told us that it is experiencing difficulty in manufacturing a combination of aloes and phenolphthalein that would be comparable in size to the present aloes-podophyllin combination. As a consequence, it has experimented with an aloin-phenolphthalein combination but clinical data must be obtained and the manufacturing process and specifications for a new formula have not been worked out.

Further, the firm is exploring other active ingredients which have been tentatively placed in Category I, safe and effective, as possible alternatives to a reformulated product.

As I noted in the recent hearings before your Committee, Category II products, whether so designated because of a lack of evidence of safety or of effectiveness, will be removed from marketing when the monograph is final. The exceptions to this will be cases in which an ingredient represents an imminent hazard to health, which is not the case in this instance.

We hope this information is helpful.

Sincerely yours,

ALEXANDER M. SCHMIDT, M.D.,
Commissioner of Food and Drugs.

Enclosure.

CARTER PRODUCTS,
Cranbury, N.J. November 8, 1974.

MR. JOHN MCELROY,
OTC Drug Product Evaluation Staff,
U.S. Food and Drug Administration,
Bureau of Drugs,
Rockville, Md.

DEAR MR. MCELROY: Enclosed please find eight (8) copies of a communication addressed to the OTC Review Panel on Laxative, Anti-diarrheal, Emetic and Anti-emetic Drugs regarding CARTER'S LITTLE PILLS. A ninth copy has been sent to Dr. Hugh A Miller, the Industry Liaison Officer for The Proprietary Association.

I will appreciate it if you will deliver these copies on or before the Panel's next ad hoc meeting, planned for November 11, 1974. We will be pleased to make an oral presentation at the convenience of the Panel, if desired. Thank you.

Sincerely yours,

DAVID A. SCHLICHTING, Ph. D.,
Director, Proprietary Drug Research.

To: OTC review panel on laxative, antidiarrheal, emetic and antiemetic drugs.
From: Carter Products Division, Carter-Wallace, Inc., Cranbury, N.J.
Subject: Carter's Little Pills.

We were surprised to learn from Dr. Hugh A. Miller that the Panel now plans to review and categorize laxative combination products. Since the second ad hoc meeting is expected to be concerned with this subject, we want to bring some new information to your attention. We will briefly summarize it here so that you may review the subject quickly, but if you desire detailed information, we will be pleased to prepare a supplement to our original submission.

Carter's Little Pills presently contain aloes (16 mg) and podophyllin (4 mg). The panel has recommended that podophyllin be placed in Category II. In light of that decision we are making plans to retain our pill form but to change our present formula to aloin (8 mg) and phenolphthalein (16 mg). We have had a product of that formula on the market in Canada, England, Switzerland and New Zealand for a number of years. We also have animal and human safety and efficacy data on the individual ingredients and the combination. We present this information in summary below and respectfully request that you review and categorize this combination.

The first consideration is the question of the activity and uniformity of aloin. The laxative activity of both aloin and phenolphthalein in rats was demonstrated in 1933 (1). We have improved on the model and have shown a dose-response relationship for both aloin and phenolphthalein. The test involves the controlled use of a corn meal diet that gives uniform G.I. tract contents and the use of a carefully constructed scale for scoring the consistency of a uniform length of exposed intestional contents. The scoring scale used is from 8 = watery to 0 = very hard and pelletized stools. The table below gives the results, indicating that the individual ingredients are active but the combination is more active.

LAXATIVE ACTIVITY IN RATS

	Dose range in mg/kg	Score range	Significance versus placebo
Placebo	0	4. 0–4. 5	
Aloin	12. 6–50	5. 1–5. 9	$p<0.05$
Phenolphthalein	50. 0–200	5. 2–5. 7	$p<.05$
Aloin/phenolphthalein	10/20–50/100	5. 1–7. 6	(1)

[1] This could not be compared statistically because it was done in a separate experiment, but by inspection is obviously greater than either ingredient alone.

The uniformity of different lots of aloin NF XI has been established in our laboratories both chemically and biologically. Chemically, the product is assayed by ultraviolet spectrophotometry and the assay has been within ±5% for the nine lots of aloin received in the last three years. The product itself is acceptable only if the product assay is within 10% of the labelled amount, i.e., 7.2–8.8 mg per pill. Biologically, we have assayed two lots from different suppliers, as described above, and obtained essentially the same slope and levels of activity for both.

The safety of the ingredients alone has been studied in rats. Reported attempts to determine in LD_{50} have been unsuccessful. A maximum tolerated acute oral dose has been reported in the literature for aloin as 7.5 g/kg and for phenolphthalein as 7.0 g/kg (1). Our own attempts to obtain LD_{50} values have also been unsuccessful due to its low toxicity. We gave acute oral doses as high as 5.0 g/kg for aloin and 5.0 g/kg for phenolphthalein in mice and were unable to obtain an LD_{50}. We obtained the same results with a 1:2 ratio of aloin/phenolphthalein at the same doses. Oral doses of up to 3.0 g/kg of both materials in dogs have been reported with no deaths or adverse reactions. These results indicate that the ingredients alone and in combination as well within the acceptable levels of safety and, in fact, approach the safety levels of foods.

Four clinical studies done by three different clinicians on 129 subjects are reported here. The first study, by Chapman, D.D. and Pitelli, J.J., *Curr. Therap. Res., 16*, 817–820 (1974) demonstrates the efficacy of the individual ingredients and their contribution to the combination. They studied phenolphthalein (120 mg) versus aloin (60 mg) and versus phenolphthalein (60 mg) plus aloin (30 mg) and a placebo. They measured the number of bowel movements, stool consistency and transit times. The study was a double-blind Latin Square design done on 28 normal males and females with regular bowel habits. It was demonstrated that the combination produced a greater laxative effect and a shorter transit time than the individual ingredients and the placebo. All three treatments gave softer stools than the placebo.

The second study, by Burton Cahn, M.D. in 1963, was a double-blind crossover study on 26 males in which 1, 2 or 3 doses, each containing aloin 8 mg plus phenolphthalein 16 mg, were given every third day for three doses, followed by a rest period. The test product was compared with CARTER'S LITTLE PILLS. The two products were equally effective and the test product showed a trend in the dose-response relationship as follows: 1 or 2 doses were effective in 50% of the subjects and 3 doses in 65% and 1 and 2 doses showed no side effects in 92% and 3 doses showed no side effects in 85% of the instances. There were no severe side effects.

The third study, by F. H. Stern, M.D., was a double-blind study on two similar aloin and phenolphthalein formulas (two slightly different ratios) on 50 subjects, comparing this product to CARTER'S LITTLE PILLS on another 50 subjects. There were four cells of 25 subjects each in the study. The results indicated greater efficacy and fewer side effects with the test product as compared to CARTER'S LITTLE PILLS. The test product showed efficacy in 76% of the subjects with respect to stool consistency and 70% with respect to time of movement. Side effects were non-existent or minimal in 68% of the subjects.

The fourth study, by F. H. Stern, M.D., also compared the test product (8 mg aloin plus 16 mg phenolphthalein) with CARTER'S LITTLE PILLS. There were 25 subjects evaluated in each of two cells in a double-blind study. The test product showed efficacy in 88% of the subjects regarding stool consistency and 70% regarding time of movement. There were no side effects in 52% of the subjects, but data on the number with minimal side effects was not reported separately.

These clinical studies indicate that a combination of aloin one part and phenolphthalein two parts is a more effective laxative than either ingredient alone. They also indicate that pills containing 8 mg aloin plus 16 mg phenolphthalein, taken in doses of 1 to 3 pills, are at least as effective as CARTER'S LITTLE PILLS in the same doses. Side effects are relatively low.

We have presented a brief summary of the safety and efficacy of aloin and phenolphthalein. The animal data in mice, rats or dogs indicate that both ingredients are well within acceptable safety levels, individually and in combination of aloin one part plus phenolphthalein two parts. A dose-response curve or bioassay procedure has been developed indicating that both aloin and phenolphthalein alone are active and that the combination is more active. Different lots of aloin from different sources have been shown to be similar in their chemical and biological characteristics. Four clinical studies using 129 subjects have been summarized. The results indicate that the individual ingredients are active but the combination product is more active. There is a suggestion that a dose-response effect exists between 1, 2 and 3 pills. Side effects are relatively few and of an insignificant nature.

We recommend that the Panel approve the combination of aloin 8 mg plus phenolphthalein 16 mg; that the dose range for aloin be set at 8 to at least 24 mg per day and that the minimum dose for phenolphthalein be reduced to 16 mg per day.

If this information should not be found sufficient for full approval by the Panel, we would ask that you provide us with guidance concerning additional information necessary for full approval.

Respectfully submitted,

CARTER PRODUCTS DIVISION OF CARTER-WALLACE, INC.

Mr. FOUNTAIN. I am placing into the record, documents relating to the status of certain OTC oral antimotion sickness drugs, the safety of which were questioned.

[The documents referred to follow:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
OFFICE OF THE SECRETARY,
OFFICE OF THE GENERAL COUNSEL,
July 8, 1973.

To: Jean Mansur (BD–68).
From: Peter Barton Hutt (GC–1).
Subject: Rx status of cyclizine and meclizine.

After reviewing the file on this matter, I have the following comments and suggestions.

1. The laxative panel has already been formed, has held at least one meeting, and has been provided all of the safety and effectiveness data relating to these products. If we wish to do so, we could ask it to review this issue as its first priority.

2. I am unable to find in the file any indication that this is an urgent matter that could not await review by the OTC panel on an expedited basis. The draft of the memorandum is dated exactly five months ago. If it has had this low a priority in the Bureau of Drugs, I would suggest that we could wait another two or three months while the OTC review panel provides its recommendations.

3. As a general rule, we have concluded that we will handle OTC drug problems outside the OTC drug review only in the rare situation where there is an immediate health hazard or a patent fraud. If this represented an immediate health hazard, we should have moved some time ago on it. In any event, it appears to me that we should at the very minimum discuss the matter thoroughly with the OTC drug review panel and give them an opportunity to consider the matter before taking action. If the Bureau does believe that there is a critical health problem involved, however, then the matter obviously should be rushed to the Federal Register.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
July 18, 1973.

To: Gary L. Yingling, Director, OTC Staff (BD–109).
From: Office of the Assistant to the Director for Regulatory Affairs (BD–68).
Subject: Status of oral preparations containing chlorcyclizine, cyclizine, or meclizine.

Mr. Hutt has recommended that in the absence of an immediate health hazard, the Bureau's proposal to restrict these drugs to Rx be deferred until such drugs have been considered by the OTC panel on anticmetic drugs, which has already been provided safety and effectiveness data. Although the call for data listed only meclizine and dimenhydrinate, we recommend that the panel also review evidence on cyclizine (Marezine) which was published as effective for motion sickness (copy attached) in 1970.

We suggest that these drugs be given as high priority as possible in the scheme of review. You may want the OTC panel to be aware of the action the Bureau has contemplated, along with the reasons and background. Therefore, I am enclosing a copy of the draft proposal.

JEAN MANSUR.

Mr. FOUNTAIN. Mr. Hutt, I want to return to the verbatim transcript of the antiperspirant panel's March 24, 1975, meeting, from which I quoted during the hearing on Friday.

I think it is apparent that this panel had difficulty in understanding the long delay in FDA's removing a category II drug from the market after the panel had made the classification. For example, at page 2–83 of the transcript, Mr. Robert Pinco commented to you:

I think, what I understand seems to be troubling the panel is that having categorized the thing into these, the ingredients as it were, into category two, they would like to see the thing happen immediately.

In response, Mr. Hutt, you said:

We have that problem in all 17 panels. The one thing that I also insist upon is absolute uniformity of treatment.

At page 2–85 a panel member expressed the feeling that a delay in action after classification would not only permit continued marketing of products already on the market, but would also permit similar new products to enter the market. This is reflected in the following exchange at page 2–85, which I am quoting in part:

Dr.———. It is just a little dismaying to us to feel, as I feel, that as a result of our putting it into a category 2, primarily because of our concern for its hazard, we have actually encouraged its distribution in the market place.

Mr. HUTT. Well, I would not agree quite with your characterization because putting it in 2 as opposed to 3, didn't encourage it going into the market place.

Dr.———. Well, the time delay between the implementation of the final report and the final monograph—

Which I guess is an interruption—

Mr. HUTT. Well, I understand that. Which is why we have the exceptions. Without a question. The difficulty is when you start down a process of this kind, and that the law does have a concept that all of you have heard of called due process of law. The fact that a panel makes a recommendation doesn't mean it is automatically accepted.

Mr. Hutt, have other panels expressed concern about the delay in removing category II drugs from the market?

Mr. HUTT. One other panel which comes to mind raised the same type of issue as to whether implementation could or should be expedited. That was the antimicrobial 1 panel. I provided them with the same advice I have provided all panels; namely, where there is a health hazard that comes to the attention of the panel, matters can be taken out of turn, out of normal procedure, and expedited. As we have related at both of the prior two hearings this has, in fact, been done and was, in fact, done with TBS. That is the only other panel I am aware of which has raised that issue, Mr. Fountain.

Mr. FOUNTAIN. At this point we want to move on to the work of the antacid review panel. I hope we will be able, in the limited time available, to complete our questioning on that subject, with all members participating to the extent they desire.

Are there any questions at this point which any member would like to ask before I get into the antacid review panel?

Mr. DRINAN. I would like to have the material they promised us two sessions ago; namely, the curriculum vitae of the people on that panel, that would be helpful.

Mr. PINCO. That was supplied the committee at the last meeting. I can get you another copy.

Mr. HUTT. I believe those CV's did not include the additional experts who were brought in, Father Drinan. That will be provided as soon as we can get that.

[NOTE.—This information was not provided by FDA.]

Mr. FOUNTAIN. Again I would like to emphasize that in our discussion of specific antacids, this subcommittee has no opinion regarding their safety or whether they are misbranded. We are interested in developing the facts bearing on the work of the advisory committees, their decisions and recommendations, the instructions given to them, and the use the Food and Drug Administration makes of the advice received.

I believe, Dr. Schmidt, that the antacid panel was the first of the review panels FDA established. Is that correct?

Dr. SCHMIDT. That is correct.

Mr. FOUNTAIN. It is also the first review panel to have completed its work resulting in the adoption of the final order and monograph. Is that right?

Dr. SCHMIDT. Yes, sir.

Mr. FOUNTAIN. I have been told that antacids as a class are probably among the least toxic or questionable drugs when used as directed. Is that information correct?

Dr. SCHMIDT. They would certainly be among those in that category, yes.

Mr. FOUNTAIN. Then would you say they are among the category which is the least toxic?

Dr. SCHMIDT. Yes.

Mr. FOUNTAIN. I am placing a copy of FDA's January 5, 1972, notice announcing a safety and effectiveness review of the OTC antacid drug products, and requesting the submission of data and information for the known antacid drug ingredients for review.

[The document referred to follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE—FOOD AND DRUG ADMINISTRATION

Safety and Efficacy Review of Over-the-Counter Antacid Drug Products

REQUEST FOR DATA AND INFORMATION

The FDA is undertaking a review of all over-the-counter (OTC) drug products currently marketed in the United States, to determine that these OTC products are safe and effective for their labeled indications. This review will utilize expert panels working with FDA personnel.

A notice of proposed rule making outlining procedures and explaining the purpose for this review is published elsewhere in this issue of the Federal Register.

To facilitate this review and a determination as to whether an OTC drug for human use is generally recognized as safe and effective and not misbranded under its recommended conditions of use, and to provide all interested persons an opportunity to present for the consideration of the reviewing experts the best data and information available to support the stated claims for these antacid drug products we are inviting submission of data, published and unpublished, and other information pertinent to all active ingredients utilized in antacid products.

FDA is aware that the following active ingredients are used in antacid products:

Sodium bicarbonate.
Calcium carbonate.
Aluminum hydroxide.
Magnesium oxide.
Magnesium hydroxide.
Magnesium trisilicate.
Dihydroxyaluminum aminoacetate.

Interested parties are also invited to submit data on any other active antacid ingredients which they may wish to be considered.

To be considered, seven copies of the data and/or views must be submitted in the following format:

OTC DRUG REVIEW INFORMATION

I. Label(s) and all labeling.
II. A statement of the complete quantitative composition of the drug.
III. Animal safety data.
A. Individual active components.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
B. Combinations of the individual active components.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
C. Finished drug product.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
IV. Human safety data.
A. Individual active components.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports (not testimonial reports).
4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.
B. Combinations of the individual active components.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports (not testimonial reports).
4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.
C. Finished drug product.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports (not testimonial reports).
4. Pertinent marketing experiences that may influence a determination as to the safety of the finished drug product.

V. Efficacy data.
A. Individual active components.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports (not testimonial reports).
B. Combinations of the individual active components.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports (not testimonial reports).
C. Finished drug product.
1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports (not testimonial reports).

VI. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.

Data should be submitted to:

Food and Drug Administration, Bureau of Drugs, OTC Drug Products Evaluation Staff (BD–106), 5600 Fishers Lane, Rockville, Maryland 20852.

These data shall be submitted within 30 days from date of this publication. (Federal Food, Drug, and Cosmetic Act, sec. 701; 21 U.S.C. 371)

Dated: December 30, 1971.

CHARLES C. EDWARDS,
Commissioner of
Food and Drugs.

[FR Doc. 72-148 Filed 1-4-72; 8:51 am]

Mr. FOUNTAIN. Was the antacid review panel established soon after January 5, 1972.

Mr. HUTT. It was almost simultaneous, Mr. Chairman. I think it was simultaneous. I believe the call for data appeared in the same issue of the Federal Register.

Mr. FOUNTAIN. I am also placing in the record the minutes of the antacid panel's second meeting which took place on May 8, 1972.

[The document referred to follows:]

FOOD AND DRUG ADMINISTRATION, BUREAU OF DRUGS, OTC PANEL ON ANTACIDS SECOND MEETING, PARKLAWN OFFICE BUILDING, ROCKVILLE, MD.

MAY 8, 1972—CONFERENCE ROOM C

Chairman, F. J. Ingelfinger, M.D. Panel members present: H. C. Ansel, Ph.D.; S. C. Harvey, Ph.D.; E. W. Moore, M.D.; H. M. Spiro, M.D.; executive secretary, G. Rosenstein, M.D.; consultant, Philip M. Berman, M.D. for J.B. Kirsner, M.D. (panelist); liaison representatives: industry, J. Pisani, M.D.; consumer, A. Dickinson.

FDA Participants—Part time: Commissioner Edwards; P. B. Hutt, Esq.; H. E. Simmons, M.D.; M. Novitch, M.D.; P. G. Walters, M.D.; G. L. Yingling, Esq.

These summary minutes are for the May 8, 1972, Antacid Review Panel. They were approved and adopted on March 1, 1973.

The various positions taken during the meeting are provisional in nature and may be modified or otherwise revised during subsequent deliberations of the Panel.

Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Executive Secretary, Consultants, or any Industry or Consumer Liaison representative.

FRANZ J. INGELFINGER, M.D.
Chairman.

INTRODUCTION

The meeting was opened by Commissioner Edwards, who emphasized the importance of the OTC undertaking and that of the antacid panel as the first OTC panel to meet. He explained the integral operations of the OTC Steering Com-

mittee headed by Dr. Jack Moxley. He emphasized that "the Panel exercises total independence in the judgments they would make. In the final analysis, the decisions are the panel's decisions". He charged the panel with "reviewing good hard scientific data, if available, and if not available, using the panel's good scientific judgment".

Mr. Hutt distributed to each participant "The Procedures for Classification of OTC Drugs" signed earlier by Commissioner Edwards (published in FR 5/11/72). He discussed the regulations in terms of safety, effectiveness, and combination drugs.

SUMMARY NOTES OF THE ANTACID PANEL

The Panel concurred in the following statements after discussion of each issue:

1. From the viewpoint of safety, the quantitative composition of the active ingredients in a drug product should be displayed on the label.

2. When sodium bicarbonate is used as an antacid, ten grams is the limit that should be taken in twenty-four hours and the label should state: "Do not use if you have heart disease, high blood pressure, kidney disease, liver disease or are pregnant."

3. Sodium carbonate can be safely used in antacid products provided it is given with acidic ingredients such as citric or tartaric acid which produces a fizz and results in a pH less than 8 (pH of sodium bicarbonate).

4. Magnesium salt containing antacids need not be limited as to the amount taken for fear of magnesium ion toxicity.

5. Magnesium Sulfate does not have antacid properties and there is no rationale for combining this ingredient with antacids.

6. The Panel believes there is no rationale in adding a laxative to an antacid unless the laxative is specifically relevant to the action of the antacid.

7. Although magnesium trisilicate is generally considered to be safe when taken by mouth, a question of silicious nephrolith following chronic use of the drug has arisen.

8. Antacid preparations should be labeled to express the following idea: "If taking prescription medication, consult your pharmacist or physician, since this product may interfere with the effectiveness of certain prescribed medications."

9. The Panel requested that experts in renal disorders, acid base balance, hypertension and nutrition be contacted with regards to levels of salt and sodium bicarbonate that should be permitted over normal intake. Dr. Ingelfinger will initiate such requests.

10. The Industry Liaison representative accepted the responsibility of obtaining additional views as to the efficacy or advantages of effervescent products. The initial response is to be in writing. Subsequently, an invitation may be extended to meet with the Panel.

11. The Panel will consider making a determination about the advisability of using lactose in antacids at future meetings.

12. The use of a bicarbonate for an antacid will be discussed at a future meeting.

13. Tartrates will be discussed at a future meeting.

Future meetings in Washington, D.C. were scheduled for: June 21–23, August 10–12, September 7–9.

Dr. Ingelfinger will make and distribute assignments regarding the submitted data which he will distribute later.

Dr. Lamar, Bureau of Drugs, will be requested to meet with the Panel in June regarding the relationship of magnesium trisilicate and renal calculi.

Mr. FOUNTAIN. I shall quote from the first paragraph of the introduction:

The meeting was opened by Commissioner Edwards, who emphasized the importance of the OTC undertaking and that of the antacid panel as the first OTC panel to meet. * * * He emphasized that "the Panel exercises total independence in the judgments they would make. In the final analysis, the decisions are the panel's decisions." He charged the panel with "reviewing good hard scientific data, if available, and if not available using the panel's good scientific judgment."

What interests me is Dr. Edwards' charge that the panel exercises total independence in the judgments they would make.

Did any FDA personnel, including of course the staff of the General Counsel's office, give any instructions or otherwise communicate with

the panel while its judgments were being formed, or after they had been formed?

Mr. HUTT. Yes, Mr. Chairman.

Mr. FOUNTAIN. What was the purpose of that communication?

Mr. HUTT. There was constant communication. The entire concept of having advisory committees for the Food and Drug Administration, for the OTC drug review as contrasted with the use of outside committees for the NAS/NRC prescription drug review, was to have the panel staffed by Food and Drug Administration employees so we would not be subject to the same difficulties that arose in the NAS/NRC review.

Mr. FOUNTAIN. Was there any communication with the panels while their judgments were being formed?

Mr. HUTT. Yes.

Mr. FOUNTAIN. Designed to influence those judgments on any matter?

Mr. HUTT. No, not designed to influence them but designed particularly to make sure that judgments were reached on all of the issues, to begin with; second, that the reason for each one of those judgments was fully laid out; third, that all questions that were raised by anyone outside the panel, or that could occur to any of us, were fully answered; and, fourth, that there was full and complete documentation of all their judgments.

Therefore our job, not just for the antacid panel but all the panels, is to meet with the panel constantly as they are forming their judgment. As I always tell them, we have no interest in how they come out on any issue but we do want to be sure they address the issues, that they back up their decisions, that they articulate their reasons in what I have often said should be third grade English. Without that, I have pointed out to every panel—and literally up until this past week I have been meeting with them on a regular basis—without that kind of documentation and sharpening of their decision it would be much more difficult to defend in the public, in Congress, in the courts and every place else we must defend it. So there is total and constant and complete interchange between my office, the office of the OTC review, and the panels.

Mr. FOUNTAIN. To give you a further chance to elaborate, Commissioner Edwards had charged the panel, as you note, in May of 1972 with "reviewing good hard scientific data, if available and if not available using the panel's good scientific judgment."

On those occasions when FDA gave instructions or otherwise sought to influence the panel's deliberations, or to inform them, as you say, about all matters they should be concerned about, was it always to bring additional scientific information on antacids to the panel's attention?

Mr. HUTT. Mr. Chairman, as I stated, no. Quite frequently it was to point out a sentence in a report which was ambiguous or that was not immediately apparent to us as to its relevance or which was not backed up by adequate scientific data or which raised additional questions which were not fully answered by the panel.

We acted in very much the same way that the friendly prosecutor would act. I would constantly—and I have done this many, many times with every panel which has a draft report—I will take their

draft report and annotate in the margins questions which occur to me in order to get the panel to answer those questions. Each time I have done that I have pointed out that I have no interest, and no knowledge, as to what the answer should be. However, it is terribly important that they answer the question one way or the other and explain the reasons for their answer.

I would say in all the times that I have met with panels, in none of those times has it been for the purpose of reviewing scientific data.

Mr. FOUNTAIN. Then I would assume that whenever questions arose in their minds they would also call upon you——

Mr. HUTT. For legal advice, yes, sir, to explain some of the procedures or, as I did with the antiperspirant panel, to explain various options open to them.

I think, if I may just harken back to the zirconium issue, the transcript will show that when I gave the options to the panel they then asked me what they should do, and I said it was improper for me to give them an answer; that, instead, is what we were asking them to say, after which we would review their recommendations.

Mr. FOUNTAIN. As I understand it, it is generally known that serious questions concerning the safety of Alka-Seltzer, for example, were raised during the panel's deliberations.

According to our information, the panel had reservations about the safety of aspirin-antacid combinations, like Alka-Seltzer (which contain aspirin and the antacid ingredient, sodium bicarbonate), when used in treating stomach distress, such as heartburn. Is that correct?

Dr. SCHMIDT. As a blanket statement, no, it is not correct.

Mr. FOUNTAIN. They didn't have reservations about their safety?

Dr. SCHMIDT. There were questions raised from outside the panel about the whole subject of aspirin and aspirin causing gastrointestinal bleeding. There were certainly discussions of Alka-Seltzer. There were discussions of Bufferin aspirin and whether or not a product such as an effervescent sodium acetylsalicylate was associated with serious bleeding or not.

It was true that these questions were discussed.

Mr. FOUNTAIN. You are saying questions were discussed and they got a lot of outside information but the panel itself had no serious questions or reservations?

Dr. SCHMIDT. They had concern about the use of aspirin—acetylsalicylic acid—by patients with chronic gastrointestinal distress or ulcers. I think everyone has that concern.

I do not believe they had significant concern about the use of Alka-Seltzer by normal people properly and its relationship to any heavy blood loss.

Mr. FOUNTAIN. Was their concern centered in any way on the fact that acid is contraindicated when stomach ulcers exist, for example?

Dr. SCHMIDT. Certainly that was discussed and it was a concern, particularly with regard to labeling.

Mr. FOUNTAIN. The first indication that the panel had considered the safety of aspirin-antacid combinations appears in the minutes of the panel's fifth meeting on September 7 to 9, 1972. I am placing those minutes in the record.

[The minutes referred to follow:]

BUREAU OF DRUGS, OTC PANEL ON ANTACIDS—FIFTH MEETING, PARKLAWN OFFICE BUILDING, ROCKVILLE, MD.

SEPTEMBER 7/9, 1972

Chairman, F. J. Ingelfinger, M.D.; members of the panel present: H. C. Ansel, Ph. D.; S. C. Harvey, Ph. D.; E. W. Moore, M.D.; J. F. Morrissey, M.D.; H. M. Spiro, M.D. (6/23); M. I. Grossman, M.D.; Acting executive secretary, A. M. Welch.

Industry scientific representatives: R. C. Brogle, Ph. D.; W. H. Feinstone, Sc. D.; K. K. Kimura, Ph. D., M.D.; J. C. Krantz, Ph. D.; H. A. Miller, M.D.; C. G. Pitkin, R. Ph.; G. Swenson, R. Ph., S.J.D.; liaison representatives: industry, J. Pisani, M.D.; consumer, A. Dickinson. FDA participants: M. Novitch, M.D.; G. Yingling, Esq.

These summary minutes for the September 7/9, 1972 meetings of the Antacid OTC Review Panel were approved and adopted on March 1, 1973.

The various positions taken during the meeting are provisional in nature and may be modified or otherwise revised during subsequent deliberations of the panel.

Whenever there is a lack of unanimity on any given point, the vote will be given. Regulations do not permit voting by the Executive Secretary, Consultants, or any Industry or Consumer Liaison representative.

FRANZ J. INGELFINGER, M.D.
Chairman.

The Panel reviewed the draft minutes for the third meeting (June 21/23) and the fourth meeting (August 10/12). Both were adopted with a proviso that the minutes for the August meeting included tentative statements for Phosphates and Evaluation of Efficacy which are to be reviewed in detail during this the fifth session.

Modifications or additions to previous statements as well as new statements are attached.

INDUSTRY SCIENTIFIC REPRESENTATIVES

A group of Industry Scientific Representatives led by Dr. Brogle met with the Panel and freely discussed with the Panel members the various statements and points that were reported to them by the Industry Liaison Representative, Dr. Pisani.

Following the meeting with the Industry Scientific Representatives, the panelists made changes and additions based either upon the discussions with the Industry Scientific Representatives, data submitted or other information available to the panelists.

CHANGES MADE IN THE ADOPTED JUNE MINUTES

Page 3: Insert after 2d sentence.

Although the Panel will not consider the pharmaceutical necessities and excipients, it is the view of the Panel that it is important that the safety of these materials and the advisability of listing them on the label be reviewed by an appropriate body. Since these materials are used in the formulation of many drugs other than antacids, it is not appropriate that they be dealt with specifically and solely in relation to antacids.

Page 3: Additional No. 4.

The Panel strongly recommends that the Food and Drug Administration grant a variance from any labeling requirement defined by this Panel only when the application for variance is accompanied by creditable scientific evidence that the requirement does not correctly apply to the product in question and which proof is also acceptable to a majority of a panel of no fewer than five disinterested consultants.

Page 3: Additional item 5.

Some antacid products may cause a laxative effect and/or constipation. Those products generally regarded as causing these effects should be so labeled. (Vote: 6 for, 1 abstained). A further statement will be drafted on the effects of individual components, effects of doses, and the need for development of standards for definition of laxation and constipation.

Page 3: Sodium, last paragraph.

This requirement does not apply to products containing less than 5 mg. (0.2 mEq.). The quoted statement is revised to read: "Do not use without the advice of your physician if you are on a sodium restricted diet. (Vote: 6 for, 1 abstained).

Page 4: Magnesium ii.

"May cause diarrhea" changed to "May have laxative effect." (Vote: 5 for, 2 abstained).

Page 4: Calcium.

To be added, "Some products, depending on their ingredients may cause constipation and should be so labeled."

Page 5: Aluminum.

The first sentence would be modified to say: The Panel considers aluminum compounds taken in OTC antacids to be safe in the amounts usually taken orally in such products and does not feel it necessary to impose a limitation.

CHANGES MADE IN THE ADOPTED AUGUST MINUTES

The Panel voted not to make a statement concerning the number of antacid ingredients in a product (Vote: 6 for, 1 opposed).

Page 5: Item 1—2d paragraph.

Delete entire parenthetical statement (Vote: 6 for deletion, 1 opposed).

Page 6: 1st line.

Add after formulation: "And/or mode of administration."

Page 6: Item 3—2d line.

Add after Antacid: "and acid neutralizing."

Page 6: Item 4 amended to read.

OTC products marketed as antacids or to relieve upper gastrointestinal symptoms should show on the label the quantitative composition with respect to all ingredients except those that are pharmaceutical necessities (see section ——). This composition is to be given per tablet, per volume unit of liquid used in expressing dose, per packet, or per packet combination. (Vote: 5 for, 2 opposed).

Page 6: Item 5.

Delete (Vote: 5 for, 2 opposed).

Page 6: Item 6 revised to read.

OTC products currently marketed as "antacids" are often used to treat symptoms that are not known to be related to acidity of gastric contents. These symptoms include "indigestion", "gas", "upper abdominal pressure", "full feeling", "nausea", "excessive eructations" and the like. Some of these symptoms are vague, most are poorly understood as to pathophysiological mechanism, and none are known to be caused by or alleviated by changes in gastric acidity. The Panel recommends that companies marketing products that make claims for alleviation of these or other similar symptoms should within 2 years provide evidence of efficacy of this product in relieving each symptom for which a claim is made. The evidence should be based on statistically valid clinical trials conducted by double blind methods including placebo controls. Claims for those symptoms for which such evidence has not been provided should be withdrawn.

Page 6: Item 7 revised to read.

The Panel takes the position that it is unwarranted to make claims or to print indications on the package label which link certain signs and symptoms, such as "indigestion", "gas", "sour breath", "upper abdominal pressure", "full feeling", "nausea", "stomach distress", "upset stomach", "excessive eructation", with normal or hypernormal gastric acidity, since the relationship of such signs and symptoms to gastric acidity is unknown or dubious. Furthermore, such claims or indications encourage the user to draw conclusions as to the cause or intermediation of such symptoms, a conclusion that even the medical profession is incapable of drawing at this time. Therefore, the Panel recommends that these claims and indications which link these symptoms to acidity not be permitted until such time as a relationship is established (Vote: 6 for, 1 opposed).

Page 7: Item 1 under standards.

Delete.

Page 8: Last sentence amended.

The Panel believes that the presently available information on the effect of calcium on the stimulation of gastric secretion does not merit further restriction on the use of calcium-containing antacids. However, as more information becomes available, such a recommendation may well become appropriate.

Pages 7 and 8: August 10/12, 1972 minutes revised to read.

Measurement of neutralizing capacity of antacids.

Materials.—Antacid, 0.1 N HCl, 1.0 N HCl, Standardizing buffer pH 4.0 (0.05 M potassium hydrogen phthalate), pH meter, magnetic stirrer, magnetic stirring bars (25 mm long, 9 mm diameter), 100 ml beakers (45 mm inside diameter), 50 ml buret, buret stand, 50 ml pipet calibrated to deliver.

Procedure:

1. Standardize pH meter at pH 4.0 with standardizing buffer and at pH 1.1 with 0.1 N HCl.
2. Pipet 50 ml 0.1 N HCl into 100 ml beaker.
3. Place on stirrer, add stirring bar, stir at 240 rpm throughout.
4. Insert electrodes, verify that pH is 1.1.
5. Add 1 unit dose of antacid. If antacid is in tablet form, add whole tablets.
6. Stir for exactly 10 min.
7. Read and record pH.
8. If pH is 3.5 or greater, proceed; if pH is below 3.5, stop test.
9. If pH at Step 7 is 3.5 or greater, add 1.0 N HCl from buret to bring pH to 3.5. Continue to add 1.0 N HCl at the rate required to hold pH at 3.5.
10. Exactly 5 minutes after beginning addition of 1.0 N HCl (15 min. after adding antacid) read and record ml of 1.0 N HCl used.
11. Calculation: 5 mEq (in 50 ml 0.1 N HCl used in 1st 10 min.)+number of ml 1.0 N HCl added during period 10 to 15 min.=mEq acid neutralized in 15 min.

Criterion 1: If pH is 3.5 or greater at end of initial 10 min. period, product may be labeled antacid.

The Neutralizing Capacity of an antacid product should be expressed per unit dose recommended on the label, or per minimum unit dose if more than one dose is suggested.

Criterion 2: If antacid passes Criterion 1, neutralizing capacity as calculated in Step 11 must be stated in package insert of ethically promoted products.

The neutralizing capacity of an antacid product is to be given in the package insert of ethically promoted products but that this information should not be given on the label of OTC products (Vote: 5 for, 1 opposed, 1 abstained).

August addendum to June minutes modified to read.

All OTC antacids should show on the label the sodium content. The sodium content is to be expressed per tablet, per packet or packet combination, or for suspension in volume unit used for expressing unit dose (see sodium, page 3). This requirement does not apply to products containing less than 5 milligrams (0.2 mEq) per unit dose.

Additional positions adopted or discussed.

Various types of burning distress felt in the upper abdomen retrosternally or in the throat may be related to the regurgitation of acid gastric contents into the esophagus, or to other and poorly understood mechanisms in which gastric acid is involved. The Panel, therefore, believes that effective antacids (see section ——) may be promoted to alleviate such symptoms as "heartburn", "sour stomach" and "acid indigestion." The Panel, however, does not approve of the use of the term "hyperacidity" unless such a condition has been substantiated.

All antacids are antipeptic in the sense that peptic activity is reduced as pH increases and pepsin is irreversibly inactivated at pH's above 7. Some antacids may have antipeptic action additional to that resulting from antacid action. No claim for antipeptic activity should be allowed unless it is substantiated by scientifically valid *in vitro* tests showing that the antipeptic action of the agent in question is substantially greater than that of an agent with only antacid action (such as sodium bicarbonate). There are conflicting reports on the efficacy in treatment of peptic ulcer of agents that are antipeptic but not antacid

(example, sulfates dextran). The Panel is not aware of any studies showing that addition of an antipeptic agent to an antacid increases its efficacy in treatment of peptic ulcer or other conditions.

The Panel regards as unjustified by evidence currently available to it the description of antacids as "floating, coating, or demulcent." The continued use of such adjectives, or ones closely allied to them, will require additional studies to confirm the claimed specific action. While the Panel recognizes that the addition of anti-foaming agents to antacids may indeed endow such products with anti-foaming characteristics, it does not now recognize any enhancement of antacid action arising from this additional capability in an antacid product.

The Panel believes that there is no valid scientific evidence that the addition to an OTC antacid of a drug which is not an antacid or a corrective for an antacid side effect will result in a mixture which will have increased safety or effectiveness for use in antacid therapy, but in fact, may reduce the safety or effectiveness of the antacid product. The use of such mixtures should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both an antacid and the added drug. This limitation should be clearly indicated on the product label. (Vote: 4 for, 1 against, 2 not present).

The Panel believes that it is irrational to add an anticholinergic drug to an OTC antacid preparation for the following reasons: Optimal use of antacids and anticholinergic drugs requires adjustment of the dosage of each drug independently. Such combinations, regardless of their formulation, will result in products which are either unsafe or ineffective. Similar considerations should apply to a combination of sedative-hypnotic substances. (Adopted without formal action of the 5 attending panelists). Similar considerations apply to combinations of other analgesics with antacids. (No action).

Although the Panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin, it takes the position that fixed antacid-aspirin combinations should not be labeled or marketed for their antacid effects. The Panel calls attention not only to the fact that OTC antacids are sometimes zealously used, which may lead to aspirin toxicity with such combinations, but also that aspirin has a potential for damaging the gastrointestinal mucosa by mechanisms in addition to the topical action of the breaking of the mucosal barrier.

The Panel considers the addition of proteolytic agents to antacid products to be irrational. Although the role of pepsin in promoting peptic ulceration is not clearly established, it is believed that the addition of pepsin to antacid products may be potentially harmful. Similar considerations apply to the addition of bile or bile salts to antacid products.

The Panel noted that some marketed products make therapeutic claim for the carminative class of ingredients. The Panel found in reviewing the submissions that no claims for therapeutic effectiveness were made for any such ingredients, therefore, the Panel is not making a statement about these ingredients.

Mr. FOUNTAIN. Only one paragraph is devoted to the subject of the safety of the aspirin-antacid combinations such as Alka-Seltzer. That paragraph appears at page 10 and I am quoting it in full:

> Although the Panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin, it takes the position that fixed antacid-aspirin combinations should not be labeled or marketed for their antacid effects. The Panel calls attention not only to the fact that OTC antacids are sometimes zealously used, which may lead to aspirin toxicity with such combinations, but also that aspirin has a potential for damaging the gastrointestinal mucosa by mechanisms in addition to the topical action of the breaking of the mucosal barrier.

I guess you would call this a rather short statement of the matter which must have taken hours to discuss. We are given no information as to whether any special instructions had been given to the panel by FDA personnel.

We don't know from what the minutes show, whether the panel might have been influenced by agency representatives, but had any special instructions or guidance been presented by FDA during the panel's consideration of Alka-Seltzer or any similar combination, should the minutes have reflected such instructions?

Dr. SCHMIDT. You are posing a hypothetical question. The answer to the hypothetical question——

Mr. FOUNTAIN. There is nothing hypothetical about this, Doctor. This is a factual situation.

Dr. SCHMIDT. I understand your question to say that if the FDA had tried to influence the panel should that have been included in the minutes

Mr. FOUNTAIN. Right.

Dr. SCHMIDT. That is a hypothetical question. The answer to the hypothetical question is yes, certainly. I am unaware that FDA tried to influence the panel in any way in making their judgments. What the FDA has done repeatedly, as Mr. Hutt has said, is to set criteria for their decisionmaking; that is, that their decisions must be well documented, and so on. I disagree heartily with your frequently-used term that we spoke to them to influence their deliberations or such as that.

Mr. FOUNTAIN. I have not said you did that. I am simply asking questions, doctor. If I have to be the devil's advocate to do it, I shall continue to do so.

I note, for instance, that two FDA representatives, Dr. Novitch and Mr. Yingling, addressed the panel. Since the minutes are part of the official record, was it proper to exclude from the record the fact that Dr. Novitch discussed FDA's combination drug policy which could have influenced the panel's independent scientific judgment?

Mr. HUTT. May I ask, Mr. Chairman, where it states that he addressed the panel? I am not sure I understand the question.

Mr. FOUNTAIN. It does not say that.

Mr. HUTT. Did he?

Mr. FOUNTAIN. He did, yes. Our information is that he did.

Mr. HUTT. If he did he would have stated and discussed what was already in the Federal Register in terms of what the combination policy is, that is, a further explication of what is stated in the preamble to the May 11, 1972, Federal Register final regulations as well as the final regulations themselves.

Mr. FOUNTAIN. I don't know how significant it is. I am simply asking whether that fact should have been reflected in the minutes.

Mr. HUTT. If it should have been reflected it might have said, "Mr. Novitch discussed the combination drug policy," but it is impossible, as you know, in minutes to reflect the substance of everything that was said, and I doubt that that simple statement would have been terribly helpful.

I think the summary minutes are intended more to reflect whether there are true substantive points that are made rather than just someone talking to the panel.

Mr. FOUNTAIN. The fact that someone from FDA addressed the panel would seem to indicate to those who had knowledge of that fact that they were individuals of whom questions could be asked.

Mr. HUTT. Their presence as FDA participants is clearly noted in the minutes.

Dr. SCHMIDT. These meetings can go on for 2 days, and minutes certainly do not include every exchange or every question and answer because, gosh, the panel members can ask for clarification of the combination policy or any number of things.

Minutes are to include substantive discussions, particularly conclusions, recommendations, votes, and this sort of thing.

Mr. HUTT. This particular meeting took 3 days.

Mr. DRINAN. This is very relevant to the question of closing all of the deliberative portions of the meetings or hearings of the advisory committee. I have before me the Federal Register of June 4, 1974, where the reasons the Commissioner closed these meetings are set forth. In all candor this is not really satisfactory to me.

When the committee comes to the portion where they actually deliberate and decide, the Commissioner, pursuant to law, says "I am not going to release the transcript of what is transpiring here." The reasons given, aside from the legal one, that this is within his power, is that somehow the panel would be inhibited.

Was the panel ever polled as to whether they desire secrecy?

Mr. HUTT. Yes, Father Drinan. It was discussed fully within the antacid panel. Indeed it was discussed fully with the chairman before he agreed to serve.

A number of the scientists, both on that panel and on subsequent panels, indicated that if it were to be held in open session constantly that they would not be interested in participating because they believe it would get bogged down with endless interruptions. In addition to that, scientists who might be willing to criticize some of the work of their brethren, and so forth, in private would not wish to get into that kind of discussion in public.

Mr. DRINAN. That is not the reason given in the Federal Register. It said this group would be inhibited. Were they asked whether they would be inhibited?

Mr. HUTT. That is precisely the answer I just gave.

Mr. DRINAN. Why would they be inhibited?

Mr. HUTT. Because they would not wish to discuss some of the scientific work that has been done in an open public forum that they might wish to give as a private opinion, in closed discussion.

On top of that I think it is fairly well known that any group which discusses the subject as it becomes more cohesive and as the people get to know each other are able to work together and exchange views——

Mr. DRINAN. That is not a reason, as I understand it, to allow secrecy. The reason you gave is that the deliberations are based on internal communications, and you cite the Freedom of Information Act. That is a particular exemption, exemption 5.

Mr. HUTT. That is correct.

Mr. DRINAN. Therefore, are you stating formally that everything that was being discussed here in this advisory committee was based upon internal communications and that they are privileged?

Mr. HUTT. Father Drinan, the two go together. The basis for the internal communication privilege under the Freedom of Information Act, as laid out in the legislative history of that act, is to afford free and open discussion within the Government.

These people are Government employees. They are not private citizens when they engage in this advisory committee work. They are Government employees; that is, special Government employees.

The issue that you raise has been raised in the courts in a case *Smart* v. *Food and Drug Administration,* decided by the U.S. district court in California. The opinion of the judge states as follows:

> Advisory committees are policy-determining groups whose deliberations are entitled to protection. The Freedom of Information Act was never intended to invade the privacy of discussions of this sort.

In connection with that lawsuit we presented affidavits to the court showing that the members of advisory committees had been consulted on this question of whether their discussion would be inhibited, and they felt that it would be. They felt it would be contrary to the public interest and to their deliberations to open up all the discussion to public scrutiny.

Mr. DRINAN. Maybe they were wrong. You can follow the court and get a reason and they sustain the exemption, but in your personal judgment were these people on an advisory panel ill-advised? The Commissioner went along with them and said secrecy would avoid undue interference with this process.

What is the undue interference? Is it industry, consumers? What is it?

Dr. SCHMIDT. Undue interference would be the knowledge that anything they said, however tentative, however exploratory, however critical, however anything, could be spread in the public press with far more harm resulting than good.

The idea of postulating, of trying things out to see what the other panel members said, this would be inhibited.

The critical examination of scientific work by their colleagues, as Mr. Hutt just said, would be inhibited.

This kind of discussion, it has been agreed over and over, is properly held in confidence.

The important thing is that their conclusions and their recommendations and the reasons for these be made public. That is what is important.

That somebody came up with an idea to try out which might prove to be an embarrassment all the way around is not significant. That there be absolutely unimpeded discussion of all the issues is terribly important.

Congress certainly has defended the right to debate policy, and so on, in private sessions, and does to this day.

Mr. DRINAN. The Freedom of Information Act permits this exemption. It may be that the Congress did not intend such a wide loophole. It still appears to me that at the moment of truth we do not have the transcript of the basic deliberations from which there emerged these key recommendations.

I yield back to the chairman.

Mr. FOUNTAIN. Mr. Hutt, you made reference to a court opinion. Which one was that?

Mr. HUTT. *Smart* v. *Food and Drug Administration.*

Mr. FOUNTAIN. Was that a written opinion?

Mr. HUTT. No, it was an oral opinion delivered April 19, 1974, by the Hon. Robert Schnacke, U.S. district court judge for the northern district of California.

Mr. FOUNTAIN. Tell us in substance precisely what he said. You say this was off the bench and not written out?

Mr. HUTT. Yes. In substance what he said was that he dismissed the suit brought by an individual who had asked that the advisory committee transcripts be released, and who was also contending, in effect, that the advisory committee proceeding should be conducted in public, not in private; that is, not closed.

Mr. DRINAN. He was a citizen in California who was a former—a consumer grouper?

Mr. HUTT. No, a former employee of the Food and Drug Administration who had retired.

Mr. DRINAN. What is his basic reason as to why he feels it should have been public?

Mr. HUTT. He felt that the Freedom of Information Act and the Federal Advisory Committee Act requires that. The court ruled they did not.

Mr. FUQUA. Mr. Hutt, is there not a similar case relating to the National Institute of Health relating to reviews of grants, and holding that they were exempt under the Freedom of Information Act?

Mr. HUTT. Yes. The rationale of the *Smart* decision was upheld basically by the U.S. Court of Appeals for the District of Columbia Circuit just recently in the *Washington Research Institute* case, which held that the so-called pink sheets, the internal review of grant applications by outside advisory committees, are not available for release under the Freedom of Information Act. It is the identical principle involved.

Mr. DRINAN. Mr. Hutt, was the *Smart* decision decided before the amendments to the Freedom of Information Act became operative over the veto of the President?

Mr. HUTT. It was decided before but those amendments, Father Drinan, do not relate to this particular exemption, as you know. They would be irrelevant.

Mr. FOUNTAIN. Mr. Hutt, I understand there has been another case decided between the two cases you cite, *Gates* v. *Schlesinger* in the U.S. district court.

Mr. HUTT. That was a Department of Defense case.

Mr. FOUNTAIN. I am advised that in that opinion they said advisory committees are not part of the agency and, therefore, not subject to the Freedom of Information Act. Is that right?

Mr. HUTT. In effect that case was overruled by the U.S. court of appeals.

Mr. GOLDHAMMER. In the *Washington Research Institute* case, which was November of 1973, there, too, the circuit court held that the review panel of the National Institutes of Health was not part of the agency. I think you will find that very positive statement made.

Mr. HUTT. Mr. Goldhammer, my recollection is that the court held that the work product of the review committees of the National Institutes of Health was protected from public disclosure. Is that not correct?

Mr. GOLDHAMMER. Just the pink sheet.

Mr. HUTT. The pink sheet.

Mr. GOLDHAMMER. Yes.

Mr. HUTT. Those pink sheets are the product of an advisory committee to the NIH. That, I think, you will agree with me. That advisory committee, in order to prepare those pink sheets, has to sit and meet. Those meetings are closed to the public.

The court upheld that entire procedure.

Mr. GOLDHAMMER. Yes, but they also made the statement, in so many words, that the panels are not part of the agency.

I might say, Mr. Chairman, that there has been a more recent decision which involved a travel agency case. Neither one of these decisions was in the U.S. district court. The travel agency case was not a reported case.

In that case the court held that title 5, section 552(b)(5); that is, the exemption of the Freedom of Information Act requirement for disclosure to the public, did not apply at all to advisory committees.

I understand the Justice Department intends to appeal.

Mr. HUTT. That issue was squarely decided by the court of appeals, as you know, Mr. Goldhammer, in the *Washington Research Institute* case. At least for the D.C. circuit that is no longer at issue.

Mr. GOLDHAMMER. On the theory that the advisory committee is not an agency of the Government, and, therefore, its deliberations are not in the nature of interagency memorandums, which is encompassed in section 552(b)(5) of title 5.

Mr. HUTT. Mr. Goldhammer, I am not entirely certain whether an advisory committee is or is not an agency of the Government in this context. The only court of appeals in the country which has looked at the issue has said that an advisory committee can meet in closed session under the Federal Advisory Committee Act, and its work product is not subject to release under the Freedom of Information Act. It is protected under the fifth exemption from the Freedom of Information Act.

Dr. SCHMIDT. The important principle here, at least to my view, is that the product of those deliberations, the conclusions, and recommendations—the things which would impact on the outside world—and the reasons for them, must be public and explained publicly. It is just how they get there, the trial and error, that is not being laid out on the public record. I do not believe that this is any more significant than are the deliberations of the Supreme Court before they render a verdict be done in public. That is not done in public.

There are many, many types of deliberations which are not done in public because of the chilling effect that that would have on the quality of those deliberations. However, I believe the end product must be public.

Mr. FOUNTAIN. I think it would depend upon the subject matter. I am not sure what an opinion of the court making reference to advisory committees would necessarily mean, if it did not relate to the subject matter in a particular case. It might be giving an opinion only about advisory committees in that particular factual situation. I don't know because I have not read these opinions.

Mr. DRINAN. Going back to something which is very important, in view of this discussion, in the Federal Register of April 5, 1973, it is indicated that two nonvoting liaison representatives were appointed to the advisory committee, one, Ms. Annette Dickinson, named by an ad hoc group of consumer organizations, and Dr. Pisani, nominated by the Proprietary Association, whatever that is.

Are these representatives employees of the Government, and who decides they are nonvoting, and can they reveal, if they desire, what went on in the deliberative sessions?

Mr. HUTT. They are members of the committee. They do sit through all sessions of the committee except where a true trade secret of a highly confidential nature is involved. Father Drinan, that has been very, very rare.

For all intents and purposes they are, therefore, present during the entire discussion. They are bound by the same rules as any other member of the committee.

One of the difficulties, and I can understand——

Mr. DRINAN. Did they also agree that they wanted the session to be secret?

Mr. HUTT. Some did and some did not. There has been a difference of opinion within——

Mr. DRINAN. You told me unanimously all the members of the committee.

Mr. HUTT. I said the scientific experts, the voting members of the committee.

Mr. DRINAN. Just the voting members; I see.

Mr. HUTT. I am sorry.

Mr. DRINAN. The two nonvoting people—did they want it to be public?

Mr. HUTT. They did not vote on that issue.

Mr. DRINAN. You didn't give them a chance to vote. They were nonvoting members.

Mr. HUTT. That is right.

Mr. DRINAN. They didn't vote on that. They didn't get a chance to vote?

Mr. HUTT. That is correct. They had a chance to discuss it.

Mr. DRINAN. I see.

Mr. HUTT. In some instances the consumer representatives urged and were given an opportunity to urge that the committee hold their sessions in public. The same was true in some instances where the issue arose as to whether there should be a transcript of the closed proceedings at all where some of the committee members wished to do so and some did not. All members, whether voting or nonvoting, were allowed to discuss the issue.

The only difference between an expert and a liaison member comes down to the vote. I am unaware of any vote by any advisory committee thus far in the OTC drug review process where one vote, or even two votes, would have totally changed what happened.

Mr. DRINAN. Is it fair to say Ms. Dickinson wanted all sessions to be public, and she so stated?

Mr. HUTT. I would not be surprised. I do not know. I do not recall.

Mr. DRINAN. Dr. Pisani was nominated by the Proprietary Association. What is that?

Mr. HUTT. That is the over-the-counter drug trade association.

Mr. DRINAN. Why did you call it the Proprietary Association?

Mr. HUTT. We did not name it.

Mr. DRINAN. What was his position?

Mr. HUTT. I simply do not recall. He is vice president for medical affairs.

Mr. DRINAN. What was his position regarding secrecy? It was only the consumer representative who said this exemption should not apply?

Mr. HUTT. I do not know. Do you know that she did not want it in closed session?

Mr. DRINAN. You said that.

Mr. HUTT. I said I did not know. You seem to know that. I do not.

Mr. DRINAN. I asked a direct question. Ms. Dickinson wanted all sessions to be public?

Mr. HUTT. I said I did not know.

Mr. DRINAN. Who decided that she is a nonvoting member?

Mr. HUTT. The question of voting members and nonvoting members arose in the following way:

When OTC drug review was first more than conceptualized; that is, when we began to write down procedures, the question arose whether, because of conflict of interest, we could have any people other than just recognized independent experts.

The decision was made that it was important to have two types of input into the committee—people who would represent known consumer interests, who would be advocates rather than independent unbiased experts, and who could bring to bear the feelings of consumers about these issues; and people who could act in the same liaison and advocate capacity for the over-the-counter drug industry.

It was immediately recognized that they could not have a vote because they would not be appearing there as independent, unbiased, nonadvocate experts. They would be there in an advocate liaision function.

Therefore, in order to avoid the conflict-of-interest issue for both kinds of representatives they were included but without a vote.

Father Drinan, there is one problem, that is the lack of advisory committee regulation; and we have recognized this and it is in the process of being handled the way it should if we had been able to do everything that should have been handled 2 years ago. We at this moment have just, on Friday, sent to the Federal Register our procedural regulations which handle all of the questions that you have raised with respect to advisory committees.

We had initially drafted advisory committee regulations sometime ago. The Department of HEW asked us not to promulgate those because they were considering regulations and the Office of Management and Budget was considering regulations.

We held off. The OMB decided not to issue detailed regulations. The Department issued regulations which did not cover our regulatory use of advisory committees. Just this Friday the Commissioner signed, and this morning they were transmitted to the Office of Federal Register, the regulations governing our advisory committees.

These cover all of the matters of meetings, public notice, when meetings can be closed, when they may not be closed, and use of nonvoting consumer and industry and other liaisons.

Mr. DRINAN. What about the question of the ad hoc group of consumer organizations?

Mr. HUTT. That was formed by the consumers themselves, not by the Food and Drug Administration.

Mr. DRINAN. Which consumers?

Mr. HUTT. The Consumer Federation of America took the lead in it but it was joined also by Consumers Union, Mr. Jim Turner, Mr. Robert Choate, and the Federation of Homemakers of America, Mrs. Desmond.

Mr. DRINAN. Who organized that group?

Mr. HUTT. As its name implies—you mean the whole group?

Mr. DRINAN. How did you write to them and how did they settle upon Ms. Annette Dickinson as their representative? I have a letter from her, not entirely pertinent to this subject, but I want to know what groups named Ms. Annette Dickinson to be their representative.

Mr. HUTT. When we first began the entire process we met with the ad hoc group, which we had been meeting with on various occasions over a period of time at their request to discuss a wide variety of issues pending before the Food and Drug Administration in which these consumer groups have an interest.

At one of the meetings we described the plans for the over-the-counter drug review. We asked them if they would choose a consumer representative for nonvoting liaison purposes as a member of each——

Mr. DRINAN. What is "liaison"? Liaison with whom?

Mr. HUTT. Consumer organizations and representatives, to provide a consumer viewpoint to the panel. For example, a consumer liaison would be obligated to go back to the consumer organizations with the types of issues arising in each panel and to ask that organization and those consumer advocates whether they wished to make their views known, whether they had any particular relevant information, whether they knew of any particular serious problems that should be raised, et cetera.

Mr. DRINAN. Did Ms. Dickinson go back to her group when you closed deliberations and make known to them this would be a secret operation during the key proceedings? Did she make that known to them and did they have a reaction?

Mr. HUTT. Yes, the consumer groups by and large asked us to open those. Indeed they submitted comments on the proposal. The Commissioner concluded, for the reasons we have already discussed in some detail, that that was inappropriate.

Mr. DRINAN. Is that correspondence available?

Mr. HUTT. I am not sure it was in correspondence. I would have to go back and look and see whether there was correspondence, Father Drinan. I am sure there might have been some. If there is it is certainly available.

Mr. DRINAN. I yield back.

Mr. HUTT. I would like to make one thing quite clear.

The Food and Drug Administration felt quite strongly we should not pick the consumer representative or the industry representative. Obviously we should pick the independent experts from people nominated and from people that we could find ourselves.

However, we went to the consortium of consumer groups and asked them particularly that they pick the consumer representative in any way that they wished, and they did that.

In the future we have a new mechanism for doing that which we believe is a somewhat more democratic process. Beginning particularly with the biologics review, where we have the same procedure, we put a notice in the Federal Register and asked for nominations by any consumer in the country, of any individual that they would like to have considered as the consumer liaison on a panel.

Then, when we have those nominations, we send those nominations with the CV's and all the information on the nominees to any group which has previously signed up with the Food and Drug Administra-

tion to participate in the voting for the consumer representative, and selection of the consumer liaison is done through a mail ballot. So it is as democratic and as open and above board as we can possibly do it now.

When the first few representatives were chosen we had not worked out that process and we were, therefore, simply going to the consumer groups for their nominees. We accepted them without question.

Mr. FOUNTAIN. Dr. Goldberg has a question. Before he asks his question, I want to ask this:

I am curious as to what strength you give the voter groups. Is it like the United Nations where 23,000 people have the same vote that the United States has? How do you do it?

Mr. HUTT. Yes. The procedure will be that anyone who is interested in participating in the voting must satisfy the person in the Food and Drug Administration who is our principal liaison with consumer groups that it is a genuine bona fide consumer group.

Then they are placed on the voting list and they will be asked to vote every time this issue arises, Mr. Fountain.

We discussed many, many alternatives. Indeed at one of the recent meetings with consumer groups we put on the agenda the exact procedure which I have just laid out and asked them for their comments to see whether it could be improved. They offered no objections to it. They thought it was a reasonable approach.

Mr. WYDLER. A question along the same line. Why don't you accept somebody from Virginia Knauer's office or someone from the Executive Office who is appointed to represent consumer interests?

Mr. HUTT. We discussed this entire procedure with Mrs. Knauer's office when it was first established. They were very much in favor of this.

They believed that it should be someone from outside the Government, just in the same way that the industry liaison representative is someone from outside the Government.

They also believed very strongly in what we thought was the critical point, namely, that the consumers select their own representative just as the industry could, so that this would be their person and there would be no suggestion that someone else was being, in a sense, foisted upon them as their unwanted representative.

It was that principle of democratic selection which we thought was critical to making it work.

Mr. WYDLER. I often wonder by what right certain groups say they represent the consumers. That could include everybody, including me. I wondered whether the Consumers Union represents my point of view at all. It might be the opposite of my point of view on a particular matter.

I am wondering by what mysterious process a certain group becomes the spokesman for consumers.

I can understand when a company is established and they are in the business of manufacturing goods they have some obviously valid interest in that particular business, but I am trying to figure out how a certain segment of the consumer population suddenly becomes the consumer voice.

Dr. SCHMIDT. We have tried to determine all legitimate groups, as Mr. Hutt said, and trying to get around part of the problem you refer

to, by using a large number of groups. Clearly many of the consumer groups are rather self-appointed representatives of consumers.

Some of them, however, are very large, have large memberships, and are well established as those things go.

Mr. HUTT. This would include, for example, the women's part of the farm bureau and the junior league and many other widely dispersed organizations which engage in consumer affairs.

Mr. WYDLER. Neither is conservative or liberal in their orientation. They are still quite a small segment of the——

Mr. HUTT. I was not referring to conservative or liberal. They are broadly based. What I intended to say is that they are not just the people who sit in Washington and regard themselves as consumer advocates. They are spread throughout the country, and as far as we can determine, regardless of liberal or conservative tendencies, they do to the best of our ability represent the country.

Mr. FUQUA. What do you consider consumer interests?

Mr. HUTT. The interests of everyone who consumes the products that are under discussion.

Mr. FUQUA. The price of it, availability, quality? What is the consumer interest?

Mr. HUTT. I may not understand your question. The issue before this particular committee was the safety, effectiveness and proper labeling of antacid products.

Mr. FUQUA. Price was not included?

Mr. HUTT. Absolutely not.

Mr. FUQUA. Nor quality or availability?

Mr. HUTT. No, sir.

Dr. SCHMIDT. One of the interests of the consumer is in the process, how it is carried out—the procedure, and the integrity of the process. To me one of the most important reasons for having the consumer representative there is to give added legitimacy, acceptance and understanding to the final product of the panel. That is very important.

Mr. FOUNTAIN. Dr. Goldberg?

Dr. GOLDBERG. When a meeting has been closed and the record is confidential, are the industry and consumer representatives free to go back to their groups and discuss what transpires at that meeting?

Mr. HUTT. Here is the way it works. In the vast majority of situations the minutes are prepared quickly and are disseminated immediately, because the minutes do not show the individual views of individual participants, and therefore the need for closing the meeting is solved by the way the minutes are written. In short, release of the minutes does not inhibit the discussion because of the way they are prepared.

For the same reason the experts and the consumer and industry representatives are perfectly free to discuss the substance of what went on in the same way the minutes reflect the substance of what went on.

There is agreement by all participants that there will be no attribution of individual views or discussion of anything that the committee decides should not be discussed because it is premature.

There are many instances where the panel has concluded not to release minutes and not to discuss issues in public because it is premature at that stage, and in those instances all people who have participated agree to that procedure.

Dr. GOLDBERG. Then, if I understand correctly, the industry and consumer representatives are not prohibited from discussing subjects over and above those reported in the minutes as long as they do not go to the question of attribution of a particular statement or premature release of policy positions which have been taken?

Mr. HUTT. Over and above those in the minutes?

Dr. GOLDBERG. Over and above the disclosures in the minutes.

Mr. HUTT. I am not sure what that would mean, Dr. Goldberg.

Dr. GOLDBERG. The chairman already has given you one instance where a brief paragraph purportedly reflected several hours of discussion. It does not take much speculation to conclude there must have been a lot of discussion that was not reflected in the minutes.

Mr. HUTT. I see. In other words, if, for example, there was concern say about a particular scientific study and that particular concern was not reflected in the minutes, yes, it could be discussed. That would show in my judgment that the minutes should have reflected the concern about the study. However, if that was the kind of situation which arose, as long as there was no attribution of views and no violation of an agreement not to discuss something which was premature, then the experts themselves would be free to discuss that as well as the consumer and industry representatives. The answer is yes.

Again, Dr. Goldberg, as I say, unfortunately this has not yet been made public in the form of guidelines in regulations, but that will be published in the Federal Register. This particular subject is discussed in some detail in those regulations. They should be published by, roughly, June 1.

Mr. FOUNTAIN. I want to get away from this and get back to the making of the record regarding our principal purpose. I have one more question inasmuch as there have been so many questions concerning this subject.

Would it be proper for the consumer or industry to release drafts of reports before they are finalized?

Mr. HUTT. This has been a subject which has again evolved as to how it is done.

I would first say, Mr. Chairman, that the consumer and industry liaison representatives are subject to the same rules, whatever they may be, as the experts who are serving on the committee. When you ask the question that way I would first have to answer that everyone does it one way or the other way but there is no split between them.

Mr. FOUNTAIN. I would think they all should be bound by the same rules.

Mr. HUTT. Exactly. That is what the new regulations make clear.

Now, with regard to release of drafts, in the early panels, as our entire procedure was evolving, this was done informally. At the point where the committee said, "We now have a draft of a document that we would like to obtain consumer and industry feeling about on a broad basis," then we would tell the industry and consumer representatives that they were free to disseminate that in any way they wanted and to bring back to the panel any comments that consumer groups or industry groups or firms might wish to make on it, so that the panel would understand what the concerns were about that document.

We have now formalized that as a result of a couple of years' experience.

First, we have asked the panel, and they have agreed, to release the entire draft report only when it reaches a final draft stage. At that point we publish a notice in the Federal Register of its availability to any person who wishes to have it, and we put it in the hearing clerk's office.

Prior to that stage the panel may release selected small portions on which they might wish to get a particular type of comment in order to get some insight which otherwise might not readily be available. There have been some, as I said, small portions being released almost on a continuous basis by particular panels, what you might call position papers, even before they have been drafted in the form of a report.

Mr. FOUNTAIN. With respect to advisory committee meetings, whether their recommendations or conclusions are accepted or rejected, and regardless of a person's opinion about them, I think we will all agree they are important documents.

As you know, the Federal Advisory Committee Act requires the preparation of detailed minutes. I guess we could have a debate about what that means. What you do put in should be detailed, but it does not necessarily mean you have to put everything in. I would think it means detailed minutes of what transpires.

However, the minutes would seem to take on added importance in the case of antacid regulations because they have been designated under "General Comments," paragraph 3 of the FDA regulation, published in the June 4, 1974, Federal Register, as part of the administrative record.

I read from page 19863 of that issue of the Federal Register, and quote in part from paragraph 3.

> The record includes the panel reports and minutes but excludes the transcript of the panel deliberations. The Commissioner is obligated to base his conclusion with respect to a monograph on the entire administrative record. In the case of the antacid monograph, the Commissioner has not read or referred to or relied upon the words recorded in the transcript of the Antacid Panel meetings. Instead he has relied solely upon the minutes of the Panel meetings, the data and information submitted to and considered by the Panel, the Panel report, the comments submitted on the tentative final order, the transcript of and material submitted at the public hearing and the comments filed subsequent to the public hearing.

Dr. Schmidt, I think it is obvious that a great deal of material becomes part of the official record. However, the transcripts of the closed meetings when the panel deliberates is not part of the administrative record; you rely solely on the minutes for a recitation of what occurred during the meeting.

It seems to me that this would, of necessity, make it appear that the minutes do take on added importance. Would you agree to that?

Dr. SCHMIDT. Yes. The minutes to me, the minutes of the meeting which report the conclusions, the recommendations, and so on, are the significant part of the official record.

What is most important, of course, is the final report with the recommendations. The deliberations, the trial and error, the false starts, the wrong pathways, and all of this I do not need nor use in evaluating their work.

Mr. FOUNTAIN. Do you regard the 1-paragraph statement of the panel's decision on combined aspirin-antacid drugs as an adequate representation of the transcript when it omits reference to discussions

in which FDA personnel participated and might have had an impact, directly or subtly, upon the ultimate decision of the panel?

Mr. HUTT. The paragraph you read is their conclusion. It is an adequate statement of their conclusion. One simply cannot put everything that went before their conclusion into that type of a document.

Mr. DRINAN. On this precise point, under the old rules or the new rules, could Dr. Pisani be in touch with Miles Laboratories, really his employer, every hour on the hour and tell them how the secret deliberations were going?

I would assume Dr. Pisani did that, and the consumer woman also did that for her constituency.

I am wondering whether from these secret deliberations the actual wording emerged. I have the label here on this package. It is all very ambiguous to me. I raise the basic question—whether or not the new directions here, if they are new, reflect what the advisory committee recommended.

As I read the evidence, they said pretty categorically this is to be taken only for people who have two ailments and that the analgesic ingredient here is aspirin, and this is about the only major thing that was touched by this particular deliberation.

I am wondering to what extent in those deliberations they said that the minimum language that Alka Seltzer could have is thus and so, and that Dr. Pisani got some consent from his people this would be acceptable.

As you know, it is an open secret that some people think the advisory committee members submitted to the pressure of Miles Laboratories. I am not saying that. I respect their integrity.

I want to know. Unless we have some indication from those minutes we don't know what went on.

Dr. SCHMIDT. You know what went on because you have the minutes and you have their recommendations. You also have the reasons for their recommendations. I believe you have everything you need to understand how they came out and why they came out that way.

The report itself is really a good discussion of what they concluded.

Mr. DRINAN. In the actual language adopted finally which was acceptable to you, I find great ambiguity:

> Especially recommended for those symptoms after too much to eat or drink, take before bed and again upon arising.

It becomes incoherent here—

> Pain relief alone, headache or body pains, fever and muscular aches that may accompany a cold.

I don't see how any normal person, and I am a lawyer, and I don't understand that, could be expected to comprehend the meaning of that.

Mr. HUTT. I would like to talk a moment about the procedure and then come back to that. I think your first question did not indicate an understanding of the procedure.

The procedure is that we first get the recommendation of the panel through the final report, with a full scientific discussion of whatever the reasons were for their conclusions. It does not end there.

That report is published in the Federal Register as a proposal. People are entitled to come in and comment, and indeed that is

exactly what happened here on the very issue that is going to be the subject of discussion today and that has been the subject of full hearings in the Senate on two separate occasions.

Then there is, on the basis of the comment, a tentative final order in which there is an absolutely clear requirement under the Administrative Procedure Act that we lay out the comments and our responses; either we agree or disagree, and if we disagree why we disagree.

At that stage again the procedure does not end. There is an opportunity for an oral face-to-face hearing with the Commissioner at which any interested person can confront us with specific targeted issues. That was done here.

The health research group came in—Dr. Wolfe, Ms. Johnson, and a physician who disagreed with the panel recommendations. They laid out, for I believe 20 minutes, all of their disagreement.

The final stage, then, was when the Commissioner addressed each point that they made in their oral comments in the preamble to the final order.

After that final order, anyone, including the health research group, was free to take that issue to court. They chose not to do so. I doubt they were persuaded that they were wrong but apparently they concluded that we had justified what we had done to a point where a court would not regard it as unreasonable.

Mr. DRINAN. I know we will get into those issues later but I still have a doubt in my mind that if I were Dr. Pisani I would have said to the members of the advisory committee, "Would you feel this particular ambiguous language is not inconsistent with your recommendation?" If they said yes, they would not complain later on. We don't know what went on.

I yield back to the chairman.

Mr. FOUNTAIN. I realize we can all have differences of opinion about minutes and what they should contain. However, it appears to me that the minutes of the discussion of the combination antacid drug nowhere approaches the detail which would provide either you, Dr. Schmidt, the public or the courts, if the case were taken to court, with a really satisfactory indication of what actually transpired during the closed meeting.

At the sixth meeting of the antacid review panel, held on December 8 and 9, 1972, the minutes show Alka-Seltzer was again discussed in the context of its being the leading brand on the market composed of an antacid in combination with an analgesic; namely aspirin. I am placing pertinent pages of the minutes into the record.

[The material follows:]

FOOD AND DRUG ADMINISTRATION, BUREAU OF DRUGS

OTC REVIEW PANEL FOR ANTACIDS, SIXTH MEETING, DECEMBER 8 AND 9, 1972, ROCKVILLE, MD.

Chairman, F. J. Ingelfinger, M.D.
Acting Executive Secretary, A. M. Welch.
Members of the Panel Present, H. C. Ansel, Ph. D., M. I. Grossman, M.D., S. C. Harvey, Ph. D., E. W. Moore, M.D., J. F. Morrissey, M.D., and H. M. Spiro, M.D.
Liaison Representatives: Consumer—A. Dickinson; Industry—J. Pisani, M.D.
Consultants, J. B. Kirsner, M.D. (12/8 only).
FDA Participants: P. B. Hutt, Esq. (part-time); M. Novitch, M.D.; G. L. Yingling, Esq.

Industry Representatives (12/8 only):
G. Beckloff, M.D., Marion Laboratories
B. Brennan, Esq., PMA
D. Carter, M.D., Miles Laboratories
A. Cooke, M.D., Miles Laboratories
T. Fand, Ph. D., Warner-Chilcott Labs.
A. Flanagan, M.D., Warner-Chilcott Labs.
B. Misek, Ph. D., Beecham Inc.
A. Ringuette, Esq., Miles Laboratories
G. Sunshine, Esq., Stuart Pharmaceuticals

These summary minutes for the December 8/9, 1972 meeting of the Antacid OTC Review Panel were approved and adopted on March 1, 1973.

The various positions taken during the meeting are provisional in nature and may be modified or otherwise revised during subsequent deliberations of the Panel.

Whenever there is a lack of unanimity on any given point the vote will be given. Regulations do not permit voting by the Executive Secretary, Consultants, or any Industry or Consumer Liaison Representative.

FRANZ J. INGELFINGER, M.D., *Chairman.*

* * * to make claims or to use indications on the package label that the products may directly affect "nervous or emotional disturbances", "excessive smoking", "food intolerance", consumption of "alcholic beverages", "acidosis", "nervous tension headaches", "cold symptoms", and "morning sickness of pregnancy" since the relationship of such phenomena to gastric acidity is both unproven and unlikely."

21. Page 32–33, C. Drugs Combining Antacid and Other Active Ingredients.—First sentence amended to read: "Although the Panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for concurrent symptoms, it concludes that fixed antacid-aspirin combinations are irrational for antacid use alone and therefore should not be labeled or marketed for such use." (Vote 6 for, 1 against).

22. Page 30. D. Drugs Combining Antacid and Other Active Ingredients, 1. Amended to read: "The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor a corrective for an antacid side effect, will contribute to the product's safety and effectiveness for use in antacid therapy alone. The addition of non-antacid or non-corrective ingredients may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor a corrective for an antacid side effect should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and non-antacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief of both of the active ingredients. The dual indication should clearly be stated on the label and the label should include a prominently displayed warning that such a combination shall not be used for the treatment of heartburn and/or indigestion and/or sour stomach unless these symptoms are accompanied by indications for an analgesic. Such a product is not appropriate for peptic ulcer and related disorders. Any analgesic ingredient that is generally recognized as safe and effective (See Analgesic Monograph) may be used as the analgesic ingredient.

2. The Panel concludes that it is rational to include a non-antacid laxative ingredient in an antacid if the laxative is solely for the purpose of counteracting the constipating action of one or more of the antacid ingredients. Any laxative action ingredient that is generally recognized as safe and effective (See Laxative Monograph) may be used as the laxative ingredient. No labeling claim for the laxative effect would be truthful, because the amount of non-antacid laxative ingredients present should not cause laxation, but only counteract the constipating effect of the antacid.

Comment: Any other combination of antacid with non-antacid active ingredients should be permitted by the Food and Drug Administration only after it is shown that the conditions for a combination drug set out in the regulations have been met. The Panel is unaware of any other such combinations which meet these conditions at the present time.

Mr. FOUNTAIN. The verbatim transcript shows dozens of pages—and I am skipping over some items I want to cover but because of limitations of time I will put them in the record—again, the verbatim transcript shows dozens of pages of deliberations on the combination antacid analgesic products like Alka-Seltzer.

The transcript shows the panel members went round and round in their discussion, as we all do at times in some of our discussions.

It is clear they recognized a basic irrationality in using aspirin with an antacid for an antacid effect.

They also felt aspirin was contraindicated when combined with an antacid for treating peptic ulcers. But when the Food and Drug personnel stressed FDA's combination drug policy, the panel sought to modify their earlier position to bring their recommendation concerning the analgestic-antacid combinations into harmony with FDA's combination drug policy, and ultimately they came up with a statement which, in effect, indicated that the panel did not believe the combination was irrational when used for treating concurrent headache and acid indigestion.

However, the panel also said that the combination of antacid and aspirin is irrational for use as an antacid alone.

Is that a fair summary of the panel's deliberations?

Dr. SCHMIDT. I think so, except that again some of your statements impugn a cause and effect relationship. Between an explanation of our combination policy by someone from the FDA on the one hand and something the panel may have done on the other, the conclusions of the panel that you read are accurate.

Mr. FOUNTAIN. Who makes policy at FDA?

Dr. SCHMIDT. Who makes policy at FDA?

Mr. FOUNTAIN. Yes.

Dr. SCHMIDT. Policy is made in a number of different levels by a number of different people. Ultimately they——

Mr. FOUNTAIN. You said some "explanation of our combination policy" at FDA.

Dr. SCHMIDT. I said someone from FDA might have explained our policy on combination drugs to the panel in order that they would know what it is and so that their deliberations, and so on, would fit within the policy of the agency.

Mr. FOUNTAIN. Referring to the panel's fifth meeting held on September 7 to 9, 1972, minutes of which are already in the record, page 6 states:

> The Panel takes the position that it is unwarranted to make claims or to print indications on the package label which link certain signs and symptoms, such as "indigestion," "gas," "sour breath," "upper abdominal pressure," "full feeling," "nausea," "stomach distress," "upset stomach," "excessive eructations," with normal or hypernormal gastric acidity, since the relationship of such signs or symptoms to gastric acidity is unknown or dubious. Furthermore, such claims or indications encourage the user to draw conclusions as to the cause or intermediation of such symptoms, a conclusion that even the medical profession is incapable of drawing at this time. Therefore, the Panel recommends that these claims and indications which link these symptoms to acidity not be permitted until such time as a relationship is established.

The vote on that was 6 to 1, 6 for and 1 opposed.

I believe these claims which the panel felt should not be permitted are being permitted to be used by the regulations, with a requirement

that evidence to support the claims be submitted within 2 years. Is that not true?

Mr. HUTT. That is true. That was their final recommendation, Mr. Chairman. That specifically was their recommendation, that they be permitted for 2 years.

Mr. FOUNTAIN. Do you regard the September 7–9 position of the panel, as I read it, a scientifically sound and reasonable one, Dr. Schmidt?

Dr. SCHMIDT. The answer to the question is "Yes," with the qualification that the science here is pretty soft science.

One of the problems that the panel had was that these words are very vague and loose terms. They are not scientific terms. The meaning to the public of these terms is questionable at best. Therefore, the panel felt that if these claims were valid they should be based on science and there should be an opportunity provided to put science underneath these terms, so to speak.

The panel set out the claims that we call category I claims, that there is some science to back the meaning of these, but that additional studies would have to be done before they could be used permanently.

Mr. FOUNTAIN. I realize that you are the final arbiter, and as head of the agency you make the final decision, and you reach that decision by due process.

I assume, also, when you call upon panels you want their best scientific advice.

The September 7–9 position of the panel with regard to the safety of the aspirin-antacid combination such as Alka-Seltzer, and the validity of the claims made, was, I assume, their best scientific judgment.

Was that not what FDA was seeking from outside experts?

Dr. SCHMIDT. This was their judgment at the time; yes. That is what we seek.

Mr. FOUNTAIN. The verbatim transcript shows that the panel was confronted or subjected to what some might call "pressure" from FDA personnel—I am not passing judgment on it but the implication is there—to get the panel to back off from its position because of the possibility that, if adopted, the panel's position might invite court challenges or conflict with FDA's combination drug regulations.

To be more specific, during the December 8, 1972, meeting there was considerable discussion on medical claims being made for Alka-Seltzer.

I am placing into the record pertinent pages of the verbatim transcript of that meeting.

[The material follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, FOOD AND DRUG ADMINISTRATION—OTC ANTACID ADVISORY PANEL

The meeting convened at 9:04 o'clock a.m., Dr. Franz J. Ingelfinger, Chairman, presiding.

(Except for FDA personnel, names of all participants have been deleted to preserve confidentiality.)

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Dr. ———. Is it related to acid?

Dr. ———. This is the point. It concerns me that we do not.

———, do you have any ideas?

Dr. ———. Would the FDA work be easier or harder if that phrase were in there?

Mr. YINGLING. I think if the word "upset stomach" does not appear that we are going to have some problems.

Dr. ———. So you would advise with no offense to my log rolling friend here your life will be easier with the phrase in than out?

Mr. YINGLING. I think so.

Dr. ———. I don't think we should be guided by that. His whole operation would be easier if it never started as far as the FDA is concerned.

Dr. ———. By easier, do you mean less lawsuits or ——

Mr. YINGLING. I disagree with that, but I mean less likely to go to the mat as the term is used. Less likely to get into litigation if a term like that is allowed. If there is no term like that, you are limiting their ability to seek to promote to a consumer who overeats or overdrinks or makes some of these other abuses.

This is a very distinct market, I think, as far as industry is concerned. It is a type of term that they have indicated can be used. You heard a very strong pitch this morning for this type of term to be left.

Dr. ———. If we leave that in——

Dr. ———. When I get on the plane, I have an upset stomach, and I have been on a boat in which lots of people have had upset stomach. And they are at the rail heaving.

Dr. ———. They are sick stomachs.

Dr. ———. I can give antihistamines and prevent this. Do you want me to go out and promote antihistamines for an upset stomach? It is the same sort of nonsense.

Dr. ———. I agree.

Dr. ———. I do, too, 110 percent.

Dr. ———. I think we are going to have to rewrite the whole section if we do this because we have now the problem what we allow in five years by subtle control tests.

Dr. ———. We are still requiring measurable antacid action. We are still requiring some kind of sensible *in vivo* studies. All we are doing is allowing the companies—we learned they apparently strongly want this kind of claim which to me is a minor thing.

Dr. ———. You are arguing on the basis of public education.

Dr. ———. Public usage.

Dr. ———. Not education, but public lack of education.

Dr. ———. Let me ask Gary if this statement which seems to be hedging a little bit, "The Panel concludes that antacids are truthfully and accurately promoted to alleviate such symptoms as," and then if any other claim is—this implies that any other claim is not truthful.

Mr. YINGLING. It surely does from the way we are reading it. In other words, if this monograph goes forward as it is written and as set up and those would be the only three claims that you would be allowed to put on an antacid product so that Alka-Seltzer and all the rest of them you have seen before you, that would be it, that would be the claim. And every product would be able to make those three claims. They would, of course, try to change their advertising. And each one would try to grab a part of the word and shuttle up their ad. But those would be the only three terms in the market place which the Agency would allow.

Dr. ———. And once Alka-Seltzer, if this actually could be implemented, changed the advertising, think of the public education that would result and to everybody. This is a medical opinion. We are approving claims which we think might be on the basis of our knowledge related to acid. We have no idea that upset stomach itself, knowing that, means anything. It would be using a criterion of what the public is saying and what the Alka-Seltzer people have advertised. The decision is related to acid.

It seems to me we have got to state what we think is medically correct and we can defend and not just because the public uses something. If the FDA can't put up with it, they can still change it. But I think we have got to stick to our principles.

Dr. ———. I would like to eliminate "sour stomach" myself.

Dr. ———. Well, obviously, we are just discussing the issue you raised with us about upset stomach. Do you want to tell why you think it is a useful phrase if I can put you on the spot?

Mr. YINGLING. Doctor, you are now on the spot, believe me.

Dr. NOVITCH. Yes, I think frankly it is the term that—I think it is the common lay term. An upset stomach, most of which is probably related to hyperacidity,

and I think that is how it is interpreted by the layman without having had the benefit of what has gone on before I walked in.

Dr. ———. Can you give any data?

Dr. NOVITCH. I can't give you any data on anything.

Dr. ———. Do you think the majority is due to hyperacidity? I really question that.

Dr. ———. I do, too. I am very, very skeptical.

Dr. ———. Particularly if you are on a boat with seasickness.

Dr. NOVITCH. I think that is one, seasickness.

Dr. ———. Most people recognize that as being something different.

Dr. ———. It is upset stomach. Add seasickness to the labeling.

Dr. ———. I don't want to prolong this all night.

Dr. ———. This extrapolates to the ridiculousness. You have to include indigestion.

Dr. ———. It is enough of a point that we have to allow everybody to———

Dr. NOVITCH. I will say that the industry people that we have heard from feel that that is how their studies—I guess as Miles reflected this morning—that is how their consumer studies show the buyers of their products interpret the symptoms as upset stomach. The whole host of them including those that are acid-related. If some are not acid-related and antacid is given, it may be in some cases inappropriate. But I think they lump all of those symptoms into the bag of upset stomach.

Dr. ———. Can't you see what will happen? There will be some kind of litigation or something like that, and they will parade a thousand people up all of whom say, "I have an upset stomach," showing doudenal ulcer patients, "I have an upset stomach." It is the kind of battle, it seems to me, we shouldn't put these folks into.

Dr. ———. The same way people with appendicitis think of upset stomach.

Dr. ———. We parade 100 intestinal obstructions. Where does this stop? Is this the only word you are going to promote?

Dr. ———. It is the only one I picked out.

Dr. ———. This is the other part that worries me.

Dr. ———. I think if we accept "upset stomach" there is nothing we wouldn't accept.

Dr. ———. You have to accept everything.

Dr. ———. That is the point.

Mrs. ———. If the other categories were products, you wouldn't have this problem.

Dr. ———. Explain that to me.

Mrs. ———. What you said just a few minutes ago, you felt very strongly this would be a real public education effort to get people to realize what symptoms were related to acidity and all this. That is what antacids are supposed to be is relievers of acid. And if we hadn't ever come up with this whole separate category of products that doesn't relieve acidity, but that relieves gastric symptoms, then you wouldn't have that category of products which you could say was good for upset stomach. And you could with a clear conscience———

Dr. ———. That is irrelevant here.

Mrs. ———. Why not?

Dr. ———. Let's assume we didn't have the other category. All this is doing is saying, "Now, if you have this symptom and upset stomach, you need something that goes for acid." Hardly and strictly defined acid category here. But it may be inappropriate.

Dr. ———. Let me ask Gary another question.

Gary, the way I see it now is that 4 people of the Panel would like to see this staying the way it is without "upset stomach" included. Two would like to see it included and one is undecided.

Dr. ———. I have now decided.

Dr. ———. Which side are you on?

Dr. ———. Stay as it is.

Dr. ———. O.K., five to two. This has to be faced.

Mr. YINGLING. I think you still have to make up short minutes of this meeting and indicate a five to two vote. And you have to put it to the Commissioner. You have given your best recommendation, and if he wants to move off, that will have to be his decision. But there it is, and it is one in which we feel there is a high potential for litigation.

That does not have to affect the decision, but the question was asked of me. And that may have to affect his decision.

Dr. ———. I think it is appropriate for us to make an additional statement here because this is so important to all of our deliberations. It is obviously controversial within our own Panel so that I think it would be appropriate to make an additional statement.

Dr. ———. It seems to me we have pretty well covered it, ———. We have given them outlets. And if they think this is the word 90 percent of the people use and they think their product is effective for this symptom, we have given them a mechanism.

I don't think it is likely, Gary, you are going to have many litigations between the two years anyway.

Dr. ———. In other words, here, say I won't accept it as antacid, but we are going to show it under the next clause or phrase, show it as a relief of symptoms which have nothing to do with the relief of acid.

Dr. ———. The Commissioner can.

Dr. ———. I think we give the FDA an out to fight litigation if they want to by recording the vote as five to two and letting it go that way. And if they want to roll one way; they go that way. And if the other way——

Dr. ———. I would like to say if it is recorded as * * *.

Mr. FOUNTAIN. One of the Alka-Seltzer labeling claims was for use in "upset stomach," and the panel was considering the suitability of a substitute for the claim. A panel member asked an FDA attorney, Mr. Yingling, whether the substitute claim would make FDA's work easier or harder if it were required to supplant the "upset stomach" claim.

Mr. Yingling replied at page 272, "I think if the word 'upset stomach' does not appear that we are going to have some problems."

This prompted another panel member to say, "I don't think we should be guided by that. His whole operation would be easier if it never started as far as FDA is concerned."

A panel member asked, "By easier, do you mean less lawsuits or—" Mr. Yingling interrupted, saying: "I disagree with that, but I mean less likely to go to the mat as the term is used. Less likely to get into litigation if a term like that is allowed."

Now, Mr.——

Mr. HUTT. Did he at any time say that for that reason they ought to change their minds? He was answering a question quite clearly—was litigation more likely if you were to go one way than another. He answered it quite accurately. Litigation was more likely.

Mr. FOUNTAIN. I am not passing judgment but just explaining what he said.

Mr. HUTT. All right. I do not want there to be any implication that he at any time suggested that was the reason for the panel to change its mind.

Mr. FOUNTAIN. The panel was convened, as I understand it, for their scientific expertise, and both you, Dr. Schmidt, and Dr. Edwards, have indicated that you wanted their independent scientific decisions.

We have noted in the transcript a number of instances where the panel was advised by FDA personnel that court contests might or would result if a given position favored by the panel were adopted.

I would like to ask—is such advice and are such statements to the panel consistent with obtaining independent and objective scientific evaluation of the products under review?

Dr. SCHMIDT. Mr. Chairman, we are operating in the real world. The court challenge to an inadequately documented, inadequately thought through recommendation by the panel would be a surety.

We have told the panel over and over again that we want their best independent scientific judgment but we want it to stick. We want it to hold up in the inevitable court challenges.

The way this is done is for them to document thoroughly the reasons for—the reasons behind—their recommendations.

I have, Mr. Hutt has, Mr. Yingling has, all of us repeatedly have told the panel that for one reason or another their recommendations must meet these certain criteria.

As Mr. Hutt says, they do not go to what the panel recommends. All of the panels are free to make whatever recommendation their expertise leads them to make.

However, we do indeed tell them what the realities of our lives are and what we must have in order to back their recommendations.

Mr. FOUNTAIN. In that process do you think you would get their objective scientific evaluations?

Dr. SCHMIDT. Absolutely.

Mr. FOUNTAIN. You do?

Dr. SCHMIDT. These people are extremely distinguished people. I know a number of them. They generally are very bright, are very egocentric. They are used to functioning in difficult situations. The idea that explaining a combination policy would unduly influence their judgment just boggles my mind.

Mr. FOUNTAIN. Why do you explain it to them?

Dr. SCHMIDT. Because it is very necessary for them to know what the combination policy is. You are quite right in getting to the heart of what is the Alka-Seltzer question, if I may, and that is whether or not there is validity to the treatment of concurrent symptoms. This gets at our combination policy.

Their recommendations would be useless if they did not conform to a stated agency policy. Therefore, they must know what that policy is.

Mr. FOUNTAIN. You make that final decision. You don't have to accept their evaluation if you don't want to.

Dr. SCHMIDT. I do not want a series of totally irrelevant judgments or recommendations from these panels.

Mr. HUTT. Mr. Chairman, I think I ought to explain what I have viewed as my role in this, also, because I have appeared now before every panel, both at the initial briefing session at which I usually talk between 2 and 3 hours giving them background information, and at subsequent sessions to explain various issues which arise.

I have become very unpopular with all of the panels, and I have told them right at the beginning of the process that they would learn not to like me very much because I am the person who must come to them constantly and say: "With regard to a specific draft report you have not done a good enough job yet because you have not explained in enough detail why you have taken positions 1 through 75."

I do not care, and I state every time I do not care, what positions they take, but they must be explained so that if and when there is a court challenge we will prevail.

There is no point in having a report that cannot be upheld in the courts.

The two specific panels which first completed their work, had hoped to make their recommendations in one instance as much as a year

earlier than it did, but largely at my insistence we held them over to complete the reports because, as initially drafted, they were not sufficient to explain the scientific reasoning.

To my knowledge, the antimicrobial I panel report, from the day we first started sharpening the language, about doubled in length.

Mr. FOUNTAIN. Again I am asking the question. FDA's policy may or may not be valid in the minds of the panel. Why should the panel be bound by FDA's combination policy?

Mr. HUTT. That is a published regulation in the Federal Register. The only way that policy can lawfully be changed is to change that published policy; i.e., to go through the same notice and comment rulemaking as when it was originally published, Mr. Fountain.

Mr. FOUNTAIN. That does not mean they may not have a right to disagree with you.

Dr. SCHMIDT. I have told the panels that if they disagree with our combination policy they are absolutely free—absolutely free—to recommend a change in that policy, and they are absolutely free in their report to make a recommendation that was not consistent with our stated policy. But it is absolutely essential that they understand what our regulations are.

At a previous hearing you were very concerned that we were not instructing our committees sufficiently and were not making them aware of our policies.

Mr. FOUNTAIN. That is right.

Dr. SCHMIDT. All right. What we are doing is making them aware of our policies.

Mr. FOUNTAIN. That does not necessarily mean that we were complaining about your not intervening and bringing certain policies to their attention for the purpose, whether it be true or not, of influencing their own scientific evaluation and judgment.

Mr. HUTT. We have not done that.

Dr. SCHMIDT. All I can do is reiterate——

Mr. FOUNTAIN. I am not saying you have. I am simply asking the question to get the record straight.

Dr. Goldberg?

Dr. GOLDBERG. What does the claim of "upset stomach" have to do with the combination policy?

Dr. SCHMIDT. "Upset stomach" was thought by some to be one symptom that is treatable by antacid drugs.

Dr. GOLDBERG. If this group felt there was no scientific basis for using a term "upset stomach" in the labeling, would it not be perfectly consistent, reasonable, and scientifically supportable for them to say that claim should be disallowed?

Mr. HUTT. Yes; and indeed that is what they did, Dr. Goldberg. The final report, and after all of the challenges to it have been finished, states that "upset stomach" is in category III. It can be used roughly for another 12 months at this stage. If it has not been the subject of adequate scientific testing at that time, it will disappear.

Dr. SCHMIDT. The issue with "upset stomach" had nothing to do with concurrent symptomatology or Alka-Seltzer. That was an issue having to do with any and all antacids—was the meaning of "upset stomach" to the people of this country related in any way to hyperacidity which could be treated by antacids? Antacids neutralize acids.

To many people it was felt that upset stomach referred to a wide variety of things, many of which had nothing to do with a low pH in the stomach.

Dr. GOLDBERG. When a member of a panel asked Mr. Yingling, of your staff, whether it would make FDA's work easier or harder if the panel were required to supplant the upset stomach claim, he replied, at page 272, "I think if the word 'upset stomach' does not appear that we are going to have some problems."

Mr. HUTT. That is correct. That was an absolutely true statement.

Dr. GOLDBERG. Isn't that influencing the panel?

Mr. HUTT. Absolutely not. The question was asked is it going to be easier or harder. The answer is it is going to be harder. That does not mean, and no one asked, and Mr. Yingling would never have said: "For that reason you, the panel, should not do the right thing."

The fact of the matter is, Dr. Goldberg, that the panel recommended it not be in category I. We accepted that recommendation and we have implemented it.

Dr. GOLDBERG. A panel member then asked, "By easier do you mean less lawsuits or——"

Mr. Yingling interrupted by saying, "I disagree with that, but I mean less likely to go to the mat as the term is used. Less likely to get into litigation if a term like that is allowed."

Mr. HUTT. Absolutely correct.

Dr. GOLDBERG. Is that not expressing an opinion on the part of FDA personnel? You testified at our last hearing——

Mr. HUTT. Wait. That is expressing an opinion, a perfectly valid, legitimate opinion with which I completely agree.

Dr. GOLDBERG. That is your opinion. You testified at our last hearing that when the antiperspirant panel asked you a question as to which of the alternatives might be more advisable, you felt that it was inappropriate for you to make any suggestions along those lines.

Mr. HUTT. The two are totally consistent, Dr. Goldberg. Mr. Yingling never said: "For that reason you ought to do the following."

If the antiperspirant panel had said to me: "Mr. Hutt, is it more likely that you will wind up in court if the panel recommends that zirconium be taken off the market?" I would have said: "Of course." That would be so obvious as to be silly not to understand that.

Dr. GOLDBERG. Why should a scientific panel be the least bit concerned about whether FDA would be taken to court? What has that to do with a scientific issue?

Mr. HUTT. What you must understand is that these people, who are sitting there—this was a 3-day meeting we are talking about here—raise all kinds of issues, some of which are totally relevant, some of which are probably irrelevant. They also, on occasion, tell jokes and relax. They are interested in understanding the whole situation.

Again, Dr. Goldberg, what did they do as a result of that discussion? They did not put it in category I.

Dr. GOLDBERG. I will get to that.

Mr. HUTT. They put it in category III.

Dr. GOLDBERG. The picture to me right now is that you have a panel sitting for 2 or 3 days. They are having interchanges with FDA personnel. Somehow or other they become intimidated from adopting

their own independent position by questions concerning whether their scientific judgment will stick, or whether FDA may have some problems.

I submit, expressing my own personal opinion, that it is of no concern in scientific decisionmaking whether the consequences of those judgments might or might not lead to litigation.

Dr. SCHMIDT. There is a purpose to this whole thing. The panel does not wish to spend a year, 3 days at a time several times a year, plus immeasurable hours at home going over these data, they do not wish to waste their time. They do not wish to be irrelevant. We do not wish them to be irrelevant to the purpose of this whole process.

I heartily disagree with your implications and your conclusions.

Mr. FOUNTAIN. Let's go ahead with the record and see——

Mr. KASTEN. If I may interject one point. A moment ago it was mentioned that the panel could have been or had been intimidated by your group or anyone else. Is there any evidence that you know of which would show where the panel, in either this group of discussions or in any of the other panel discussions, has, in fact, been intimidated in any way by your agency or your advisers?

Dr. SCHMIDT. I have heard of nothing. I assure you that one of the values, one of the great values, of the process we have established is its openness, its inclusion of the consumer representatives in those deliberations in essentially all of them.

I assure you that I would have heard about any effort to intimidate or any resulting intimidation of the panel. I know of no such circumstance. I have heard of no rumors even of such.

I would assume that if this sequence which was brought out this morning is an example of it then I think everybody can judge for themselves.

Mr. HUTT. There is one thing I would like to follow up on there. We have and will continue and must continue to very sharply act as what the chairman called not too long ago a devil's advocate.

I have on many, many occasions, and I would hope that the person who follows me will continue this or he will be in trouble, gone to a panel and said, "You put this in category III. Why don't you put it in category II? The way it is written up it looks as though it should be banned completely."

Or, "You put this in category III. Why should it not be in category I? How do you distinguish it from this other ingredient?"

I will do that. I have done it all the time. In my judgment that is not intimidating them but it is saying to them "You must do a first-rate job so that anyone who wishes to pick this report apart the way I am doing it as a devil's advocate is not going to be able to do it."

If they cannot stand up to that kind of examination and that kind of sharp questioning and if they would be "intimidated," then what that is saying is that whenever that issue got to court they would be intimidated and would not be able to back up their report.

Mr. KASTEN. It seems, at least from this morning's discussion, there have been cases in which you have given a point of view or been asked for a point of view or been asked for an opinion and they in fact have done something different from what your point of view would be. They are looking to you for advice. Is that the idea? Then with your advice, along with advice from a number of other sources, they make an independent decision. Is that the way the process works?

Mr. HUTT. That is true. Indeed, I will give you an example where I told them what they wanted us to do could not lawfully be required. They said they wanted to make a recommendation, anyway.

I said that was absolutely fine with us.

Mr. KASTEN. They went ahead, and in fact, did it?

Mr. HUTT. Yes.

Dr. SCHMIDT. The important point is that the opinions rendered by the agency are opinions which have to do with points of law, points of agency policy, responses to questions they ask, but they do not go to what the panel should decide. That is an important distinction.

When people ask us a question we will tell the truth. I have never been impressed that the truth is intimidating.

Mr. DRINAN. Let me quote the exact words of the statute which binds Congress. In the Federal Advisory Committee Act it states Congress has the right and duty of oversight and it is our duty to check on all Federal advisory committees with regard to several things, and I cite this: "We should assure that the advisory committee has in its regulations and contains appropriate provisions to assure that the advice and recommendations of the advisory committee will not be inappropriately influenced by the appointing authority but will, instead, be the result of the advisory committee's independent judgment."

I raise the central question. You had the drug industry and the consumers there. Why does the General Counsel of the agency speak to them 2 or 3 hours at a time and tell them what will wash and what will not in court? Why can't the competing parties that you have put there in a nonvoting capacity inform the committee and then the advisory committee come out with the independent judgment?

Mr. HUTT. I would be happy to respond to that. We have an obligation to make known to every panel the content of the procedural regulations which govern the entire over-the-counter drug review.

Mr. DRINAN. Dr. Pisani is capable of doing that and so are the consumers.

Mr. HUTT. No, they are not. Neither of them is a lawyer and neither of them knew the details of the procedure——

Mr. DRINAN. They are not competent, then. An advisory committee is an independent outside force which should not be doing the work of the agency.

Let me read you something else. If there is an advisory group which is really already doing the work of the agency, the advisory committee should be abolished. Now you are saying people you appoint are not competent.

Mr. HUTT. They are competent to do the job they are asked to do. You are not asking that. You are asking whether they were competent to give legal advice.

They are not. They are competent to represent the consumer interest and industry interest as advocates and liaison for those interests.

Mr. DRINAN. Why don't you put a lawyer on?

Mr. HUTT. Because in my judgment it would be highly improper to have legal advice given by an advocate for a particular viewpoint. We are obligated to enforce the statute, interpret our regulations, and apply them, and be certain they are interpreted and applied uniformly from panel to panel.

What would happen if I were to go to court with 17 different panel recommendations, each having gotten different conflicting legal advice?

Mr. DRINAN. That is not a real hypothetical.

Mr. HUTT. It would be if we did not go and talk to these people.

Mr. DRINAN. I say categorically that is an inappropriate influence by the appointing authority.

I yield back.

Mr. HUTT. I disagree with you categorically. We could not run that procedure without doing it.

Dr. SCHMIDT. Father Drinan, when somebody is to explain agency policy——

Mr. DRINAN. I am sorry. What is that?

Dr. SCHMIDT. When someone is to explain agency policies or my policies or my beliefs, then I will do that or Mr. Hutt will do that.

Ms. JORDAN. One problem we may have is seeing the timing of your commentary on what ultimately comes forth in the form of recommendations or conclusions by the advisory panel.

You come in initially to give an overview of what their work is all about?

Mr. HUTT. Yes.

Ms. JORDAN. Is your advice a continuing handholding operation? Are you commenting each step of the way with the conclusion of each recommendation? Do you say this does and this does not? What is the sequence of your involvement and interjection of comments?

Mr. HUTT. My usual procedure is as follows: I was referring to a transcript which was made of my presentation to the antimicrobial II panel on July 26, 1974, which runs some 20 single-spaced pages in length. This was the initial charge during which I literally begin with the Food and Drug Act of 1906, bringing the panel up through the 1938 act, the 1962 amendments, the National Academy of Science review, the procedures, et cetera. That takes 2 to 3 hours.

I state in the course of that several important propositions. I state, first, that what I am giving them is such a broad overview it is quite clear that when specific questions arise either I or others will be required to come back to the panel at their request whenever they wish to discuss specific issues.

Second, I state that this is quite a different procedure than scientists are accustomed to. They are not simply writing general scientific recommendations for publication in medical journals.

They are probably, and this is true of 99 percent of the participants, for the first time in their lives participating in a law enforcement effort.

This means that their recommendations must be sharpened and honed into the form of regulations which can be held up in the courts because, as I constantly say, I am interested in litigating for the sake of litigating. I want to have procedures that will work and on which we will prevail in the courts.

Inevitably they ask me to return and do that sharpening process not in the midst of their deliberations when they have nothing to sharpen but at the point where they have come up with draft reports.

As I stated earlier, in every panel where this has occurred, although I try to be somewhat humorous about it, I have made myself unpopular by forcing them to look at difficult issues in a very sharp way to say

exactly what they mean, exactly what they can say can be upheld by scientific evidence or good sound scientific judgment, and what does not meet that test.

In most instances this has not resulted in any particular change in the report, although in some instances it has.

I can recall instances where I have asked them, as I mentioned earlier, "Why is it that you do not totally ban this drug?"

In others "Why is it you permit this in category I and another one in category III? I cannot see the difference in the writeup between them. What is your scientific reasoning?"

I precede that in every instance by saying "I have no interest in what you decide. I am prepared to go to court and defend whatever it is that you recommend as long as it is backed up by good sound scientific evidence and reasoning and that reasoning is spelled out in detail."

I did that with the antacid panel, I did it with the antimicrobial I panel, I did it with the laxative panel, and the cough and cold panel. I guess that is all because I have only until Friday and I will be leaving the Government.

However, that is a terribly important process. Because, as I also explained, and many Commissioners have been unhappy with this explanation, there is no supreme court of science. It is a Supreme Court of law. It is not their scientific peers who will pick up this report and decide whether it gets implemented. It is lawyers and judges who make that decision. So it must be written and backed up in a way that it will stand up in court.

Ms. JORDAN. So you do not interject the "standing up in court" idea until a recommendation has been framed.

Mr. HUTT. I stated it in a general way in my opening charge. I would be happy if this 20-page discussion were made available to the subcommittee and included in the record.

Mr. FOUNTAIN. We will be glad to make it part of the record.

[The material referred to may be found in the appendix at pp. 337–349.]

Mr. DRINAN. How do you decide all by yourself whether it should stand up in court? Perhaps you should take something that does not seem to have all the scientific backup you think you need in a court, and maybe it is your job to take this advisory committee's independent judgment and perhaps lose in court. Why should the general counsel of the agency say, "We have no precedent here and the courts will not go that way and we will go before Judge So and So"?

If that is not an inappropriate influence then what is?

Mr. HUTT. I think you have misinterpreted me. When I say "stand up in court" I mean sufficient scientific data and reasoning, whether or not I would agree with it as an individual. I have no scientific qualifications and have never in the entire number of discussions I have had expressed any opinion on any scientific issue.

What I have said in every instance is: "If this is what you want to say, isolate the data to support your statement and spell out the reasons for it. Then I can uphold it in court."

That is what I mean.

Mr. DRINAN. You are assuming they are all going to be unanimous. You are really influencing them and pressuring them to be unanimous?

Mr. HUTT. No, sir.

Mr. DRINAN. Wait. Maybe you should take a 4 to 3 opinion and take the judgment of the four and go to court?

Mr. HUTT. I would have no difficulty in that.

Mr. DRINAN. You go in there and tell them you want facts, no confusion of facts, just give you facts and hard facts to stand up in court. You are not encouraging diversity of opinion or independent judgment.

Mr. HUTT. Father Drinan, that is a misstatement of what I have said. I have said to every panel that if they wish to have minority reports, 4 to 3 reports, that is absolutely fine with me. If any individual on any advisory committee wishes to file a dissenting opinion that is fine with me. That will not prevent me from upholding something in court.

What will prevent me from enforcing it, and I have said this to all the panels, is a lack of data and reasons. I cannot go to court and say simply seven people do not like this drug, and, therefore, we are taking it off the market.

Mr. DRINAN. You are treating them like children. If they are distinguished people obviously they will turn up scientific findings. What difference would it make if you never appeared and gave them material about the FDA and said, "Six months from now give us a report"?

Mr. HUTT. We would have inconsistencies.

Mr. DRINAN. In what?

Mr. HUTT. The report.

Mr. DRINAN. You are appointing incompetent people, then?

Mr. HUTT. Father Drinan, there are inconsistencies in Congress, too.

Mr. DRINAN. You are not satisfying this. One last question. If that is not an inappropriate influence then what is? I refer to the statute.

Mr. HUTT. I will tell you what is an inappropriate influence. It would be inappropriate for me, for any scientist in the Food and Drug Administration, to go to the panel and say, "We think you ought to take this drug off the market or put this drug on the market," or whatever. It is not inappropriate, and cannot be inappropriate, for us to ask people to point to scientific evidence to justify their conclusion and to spell out their reasoning. Anyone who is not willing to do that should not be serving, I think you would agree, on an advisory committee, or in the Government, or in Congress.

Mr. FOUNTAIN. I think I can go along with you on that.

Let me emphasize again what I said earlier. This committee, as far as I know, has no opinion regarding the safety or whether antacids are misbranded. We are interested in developing the facts bearing on the work of the advisory committees, their decisions and recommendations, instructions given to them, and the use FDA makes of advice after it is received.

As I understand it, you do not have to accept their recommendations. If you go into court you can make your defense or position on the basis of what you, as an agency, want to do.

Mr. HUTT. Yes, Mr. Chairman, there is one qualification of that. Under the recent Supreme Court decision, whatever basis exists for the final monograph must be in the administrative record. We could not go to court and try to uphold a monograph on the basis of information that has not been in the administrative record. That is why the recommendation of the advisory committee is so essential.

We could not bring new experts into the court. That would be prohibited.

Mr. FOUNTAIN. You could still on the basis of scientific knowledge in-house at FDA take a position and support that position even if you disagreed with it?

Mr. HUTT. Yes. What we can do, if we wanted, is to take the advisory committee report, literally tear it up, and start all over again ourselves. That would be a terrible waste of time and resources.

Mr. FOUNTAIN. The transcript at page 274 discloses this dialog relating to the "upset stomach" and "sour stomach" claims. I quote from pages 274 and 275 of the December 8, 1972, meeting:

> And once Alka-Seltzer, if this actually could be implemented, changed the advertising, think of the public education that would result and to everybody. This is a medical opinion. We are approving claims which we think might be on the basis of our knowledge relating to acid. We have no idea that upset stomach itself, knowing that, means anything. It would be using a criterion of what the public is saying and what the Alka-Seltzer people have advertised. The decision is related to acid.
>
> It seems to me we have got to state what we think is medically correct and we can defend and not just because the public uses something. If the FDA can't put up with it, they can still change it. But I think we have got to stick to our principles.

Another panel member then said: "I would like to eliminate 'sour stomach' myself."

A third member then questioned Mr. Yingling as follows:

> Well, obviously we are just discussing the issue you raised with us about upset stomach. Do you want to tell why you think it is a useful phrase, if I can put you on the spot?

And Mr. Yingling, at page 275, replied: "Doctor, you are now on the spot, believe me."

FDA's Dr. Novitch then added, and I quote:

> Yes, I think frankly it is the term that—I think it is the common lay term. An upset stomach, most of which is probably related to hyperacidity, and I think that is how it is interpreted by the layman without having had the benefit of what has gone before I walked in.

Dr. Novitch was asked by a panel member whether he had any data, and he replied: "I can't give you any data on anything."

The panel member pursued the point by asking: "Do you think the majority is due to hyperacidity? I really question that." Another panel member supported his position by saying: "I do, too. I am very, very skeptical." This was followed by much discussion, as reflected in the pages of the transcript I have placed into the record, in which the panel members expressed the view that almost any condition of the digestive tract could be construed as "upset stomach" from seasickness to appendicitis, to intestinal obstruction.

Dr. Novitch commented at page 276 of the transcript, and I quote:

> I will say that the industry people that we have heard from feel that that is how their studies—I guess as Miles reflected this morning—that is how their consumer studies show the buyers of their products interpret the symptoms as upset stomach. The whole host of them including those that are acid-related. If some are not acid-related and antacid is given, it may be in some cases inappropriate. But I think they lump all of those symptoms in the bag of upset stomach.

After the discussion, members of the panel expressed themselves as follows:

At page 277: "I think if we accept 'upset stomach' there is nothing we wouldn't accept."

Another panel member said: "You have to accept everything."

And a third panel member added: "That is the point."

At page 278, the chairman informed Mr. Yingling, and I quote: "Gary, the way I see it now is that four people of the Panel would like to see this staying the way it is without 'upset stomach' included. Two would like to see it included and one is undecided."

At this point the member who was undecided joined the four who preferred to see the "upset stomach" claim excluded from the labeling, at which point the chairman said: "OK, 5 to 2. This has to be faced."

Then Mr. Yingling replied, and I quote from page 278: "But there it is, and it is one in which we feel there is a high potential for litigation."

At page 279 there was discussion of the impact of the vote with respect to upset stomach and the likelihood of litigation following. One of the panel members said;:

> I think we give the FDA an out to fight litigation if they want to by recording the vote as five to two and letting it go that way. And if they want to roll one way, they go that way. And if the other way——

I have gone into detail here in order to convey the flavor of the deliberations and the effect of the representations by FDA personnel on matters which, as I see it, are not scientific and which apparently in this case had an effect on the deliberations of the panel.

Dr. Schmidt——

Mr. Hutt. Mr. Chairman, you say they had an effect. Again I come back to the fact that the panel did not change its mind.

Mr. Fountain. We will get to that.

Mr. Hutt. All right.

Mr. Fountain. Dr. Schmidt, the summary minutes are silent concerning the participation of Dr. Novitch and Mr. Yingling. Was it proper or improper for the minutes to exclude their part in the deliberations?

Dr. Schmidt. I think it was quite proper. Their presence was there. What you read took a few seconds. If everything that was said were included in the minutes that would be, in effect, verbatim. Those panels which want verbatims have them.

What was being discussed here was the meaning of the words "upset stomach" to the general public and whether there was a correlation between hyperacidity and how people felt and the words "upset stomach."

What Dr. Novitch said was what a lot of people were saying, and that's, "Well, you know to a lot of people hyperacidity is described as being an upset stomach. There are no data on this subject."

What is important is that at the end the panel rejected that as a category I claim and these discussions certainly did not influence them

I do not believe that you can get from a verbatim transcript, anyway, what was going on, whether this was relaxed, jocular kind of conversation, whether people were laughing or not. I have no idea from reading the context of even the discussions about upset stomach. Most of these were irrelevant, really, to the significant issues the panel was dealing with.

Mr. Fountain. Mr. Hutt, we do not know what went on behind the scenes, but again from a reading of the transcript of the antacid panel meeting of December 9, 1972, portions of which I am placing in the

record, the panel was advised by Mr. Yingling at page 25 of the transcript that Mr. Hutt would be visiting them.

[The material referred to follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, FOOD AND DRUG ADMINISTRATION—ANTACIDS PANEL

(Except for FDA personnel, names of all participants have been deleted to preserve confidentiality.)

PAGES 25 AND 26

Dr. NOVITCH. One way to approach it might be to not address yourselves to what is unsafe, but rather to what is safe and effective. You could say the panel concludes that the following combinations of antacids with nonantacid ingredients provide rational concurrent therapy, and then you don't have to address yourselves to what is unsafe or ineffective because they won't be generally recognized as safe and effective in any monograph.

Dr. ———. That sounds good.

Dr. ———. You mean you're ready to say—I thought we had some debate as to what simethicone does.

Dr. ———. Well, I think we'd say simethicone is generally recognized as safe.

Dr. ———. And he wants us to say not only is it safe, but rational, and therefore good and effective. The problem is, if we can't do it, we can't do it, it seems to me, and that's just so much so. I don't see why, since we have this terrible hangup here, I should think this whole paragraph should be deleted. If you want to introduce some other general statement, all right, but this is still really under phase one.

Mr. YINGLING. I think this is one area that we discussed before. Mr. Hutt would come in around 10 o'clock and since we're spending a lot of time, why don't we cross this one off and let him discuss at that time some of the needs and the agency's problems and possibly even draw up an opening type of statement that we could make use of, if that would be acceptable with you.

Dr. ———. Anything to get us out of this dilemma.

Mr. YINGLING. We'll cross off the whole paragraph for the time being.

Dr. ———. For the time being. This still deals with part one drugs.

Mr. YINGLING. That's right.

Dr. ———. In other words, the approved.

Mr. YINGLING. Right.

Ms. ———. That eliminates your statement on analgesics, right?

Dr. ———. No. There's another one later.

Mr. WELCH. It's not an elimination. It's just a delay until he comes down.

Dr. ———. Page 32(C) takes up antacids and other active ingredients.

Ms. ———. But that's under category two.

Dr. ———. Well, if it's not in category one I shouldn't think it would be—if it's not mentioned, that doesn't mean it falls naturally into category one.

PAGES 49 THROUGH 74

How about C.1: "Although the Panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for concurrent symptoms, it concludes that fixed antacid-aspirin combinations are not properly labeled or marketed for their antacid effects alone. Not only are OTC antacids sometimes indiscriminately used, which may lead to aspirin toxicity with such combinations, but aspirin also has a potential for damaging the gastro-intestinal mucosa by the topical action of breaking the mucosal barrier or by other mechanism."

This is something we debated and worked on for many hours at our last meeting.

Dr. ———. This sentence starting with "Not only," why isn't that in the same form as we have had before; namely, comment?

Dr. ———. It is comment.

Dr. ———. But it hasn't been separated.

Dr. ———. Well, it could be.

Dr. ———. Other than that, I'm in agreement with the statement.

Dr. ———. That statement prevents Alka-Seltzer from using its first indication here; is that right?

Dr. ———. Yes.

Dr. ———. I'm not at all sure that it does, because they are currently labeled as antacid-analgesic. They don't claim to be only an antacid.

Dr. ———. But "for quick relief, upset stomach, acid indigestion and heartburn, Alka-Seltzer produces a sparkly solution which reduces gastric acidity. Alka-Seltzer soothes away the discomfort of heartburn." That's as specific as the first one they talk about.

Dr. ———. But they could rewrite it a little bit.

Dr. ———. But it isn't clear to me that anything we say can cause them to label the indications as we would wish them to do so it would only be used for the combined indications. As I understand the regulation on combinations, if a significant portion of the target population has the combined indications, then they can use it for the individual indications also.

Mr. YINGLING. But it's going to have to come out of the two panels. In other words, you have allowed a certain number of statements here. So if you allow Alka-Seltzer with the tie-in together, like heartburn, sour stomach, acid indigestion. Now, if the analgesic panel allows headaches and aches and pains, they could say "for use in heartburn-aches and pains, sour stomach and headache," that type of thing. They will not be able, because they are a combination, to draw claims out of the sky and say that that's for——

Dr. ———. But I don't see how we have accomplished a thing because the Alka-Seltzer ad that says if you have heartburn take Alka-Seltzer will not be changed in any way.

Mr. YINGLING. It will have to be if you tie the claims together. If you say that the thing has to appear together, then, of course, that's the Federal Trade Commission's work on the ad, but it will have to say I think when it flashes on the screen at the end of their TV ad "upset stomach," and then in the verbal part they say "for upset stomach and if you have a headache." Well, I think in the future, if the FTC takes this thing and uses it as we see it, it will say "heartburn-analgesic," in other words, flashed on the screen at the same time without losing the analgesic claim at the back of the ad.

Dr. ———. I don't think if you were here last time when we discussed this, it was pointed out that we felt sure that the company could finagle it some way, but we felt this was as far as we could go, but if we tried to insist they at least had to put in the antacid or at least some indication—I don't know how we can go any further.

Dr. ———. You asked the question of the guy yesterday—do we believe that there's any rational place for aspirin in the treatment of heartburn?

Dr. ———. No. We say it's not indicated.

Dr. ———. I think we have to be much stronger than what we've got here. I really think we have left the door wide open and we haven't really accomplished anything.

Dr. ———. We went all through this last time.

Dr. ———. I know that. We never settled it. We are right back where we were. We haven't done anything except make them change the wording in their commercials and I think this is bad.

Dr. ———. I would like to see some way to proscribe the use of the word "antacid" here and use "heartburn with headache."

Dr. ———. I think it's worse than that. I think it should not be allowed for heartburn or headache. I think this product should be removed from the market for the purpose of being an antacid.

Dr. ———. I really go along with that.

Dr. ———. I don't think it's rational. I think it's bad.

Dr. ———. But if you have a combination, which I think you'd have to admit you do at times—some sort of symptom that's helped by aspirin and some sort of gastric distress—it seems to me it's a good combination. If you have a cold and heartburn and a little bit of fever——

Dr. ———. Do people have colds and heartburn?

Dr. ———. Yes. I do.

Dr. ———. Not because they're taking Alka-Seltzer.

Dr. ———. Well, I'm using that as an example.

Dr. ———. I'm asking, this combination—you people were at me yesterday for upset stomach which I think is a—but does the general public associate heartburn with a cold?

Dr. ———. They don't associate it, but it may happen.

Dr. ———. Upset stomach and a cold.

Dr. ———. All right. Does anybody have any specific suggestions as opposed to just saying we're not very happy with this.

Dr. ———. I agree with ———, I think we should write this so that this combination is not permitted to be used as an antacid.

Dr. ———. We think it's a damned good aspirin.

Dr. ———. You feel that the statement should read that aspirin or aspirin-like agents should not be included in any OTC antacids.

Dr. ———. Yes.

Dr. ———. You're going to deprive Dr. ——— of one thing I remember him saying in a previous meeting, patients with ulcer and arthritis.

Dr. ———. He can prescribe that as a physician.

Dr. ———. It seems to me we're sort of weighing things here. I think there are people that have headache and heartburn simultaneously, but I think the number involved is relatively small compared to the mass of people taking aspirin indiscriminately.

Dr. ———. How many people have duodenal ulcers in one way or another.

Dr. ———. About 10 percent.

Dr. ———. So there's 20 million folks. There's no evidence that aspirin is helpful in that group of the target population. It's that group of people who it seems to me most likely to be taking an antacid-aspirin combination because of the current advertising.

Dr. ———. They are the most likely to get into abuse here.

Dr. ———. And they are the ones who are most likely—I have never written the Alka-Seltzer Company, but we have all had the feeling that we have seen patients who have been taking Alka-Seltzer who have bled, and it doesn't seem to me to be any evidence that Alka-Seltzer is good for duodenal ulcers.

Dr. ———. Again, you were not convinced by this?

Dr. ———. I was convinced yesterday and I read the submission and I said this is incredible material—it's first-rate, and it is. I think it's first-rate for everything as near as I can see up to the point of peptic ulcer, and I think that all the guy gave us yesterday was his opinion. Are you aware of any studies on Alka-Seltzer and peptic ulcer as such?

Dr. ———. There was one quoted in this long review the FDA made where 135 patients admitted to a British hospital were bleeding. It was 135 people who had taken aspirin prior to bleeding, and of this number, something like 24 of them had taken Alka-Seltzer and 19 of them had only used Alka-Seltzer.

Dr. ———. I don't see how this panel—I don't want to delay things—can in the present state of knowledge accept Alka-Seltzer as a primary treatment for heartburn. To say "heartburn-antacid" seems to me to be weasling.

Mr. YINGLING. Is there some language—because you asked me the other day about going into litigation and I assure you this will take care of that—is there some indications that you would allow for a combination of this type?

Dr.———. What about putting this in Category III?

Mr. YINGLING. Well, I was going to say that's going to require more research. Are we talking about more research?

Dr.———. I don't see any purpose.

Mr. YINGLING. What about the overnight indulgence, the alcoholic, and a lot of people you talk to that seems to be the big use, after the bad night.

Dr. ———. That doesn't make sense. Your hangover comes the next morning usually.

Dr. ———. The way I look at it, it's nice to have the buffered aspirin, but for the occasional use—say somebody who needs an antacid also needs an analgesic. That's not the person you're worrying about the gastric bleeding anyway. You are worrying about the people that are talking repetitive aspirin here. So I don't see this gimmick here is critical to the safe use of aspirin.

Mr. YINGLING. I don't think there's enough dollar market to limit their sales in one area.

Dr. ———. I think 90 percent of their sales are probably as an antacid primarily, and I think they even imply that.

Dr. ———. If they sold it in two forms, with and without aspirin, they'd double their sales.

Dr. ———. They said they did that before.

Dr. ———. That was before television.

Dr. ———. That was before "Ralph."

Dr. ———. Do you feel that this first sentence with really just a slight change, if you want to pursue this—say "are not properly labeled are marketed for any antacid effect"—if that's what they want.

Dr. NOVITCH. What you're saying is no antacid claim could be made for this, just an aspirin? You're not concerned about the aspirin claim, but no antacid claim could be made either singly or in combination?

Dr. ———. That's what they're talking about now, yes.

Dr. NOVITCH. Even if you limit it to the simultaneous presence of GI and other symptoms?

Dr. ———. As I understand—and others' comments.

Dr. ———. I do have to admit what they are going to come back to is that diagram we saw up there of .1 percent complaints or whatever it is, and——

Dr. ———. But you could do that with anything.

Dr. ———. You've had more cases than they have reported and so have I and ———than they reported in their totals.

Dr. ———. It could apply to any agent you wanted to add to this. You could put it in concrete and not get side effects and it's not rational.

Dr. ———. But that kind of reporting was meaningless.

Dr. ———. I'm just trying to say if we wanted this, would that take care of it, "all marketed for any antacid effect or for antacid effects," period.

Dr. ———. Just say "for their antacid effects" and leave out the "alone."

Dr. ———. I'd say "should not be labeled or marketed."

Dr. ———. All right. This is what I'm coming to and we have got to take a vote and decide, but I want to see what the alternatives are. One thing, of course, this will settle the whole argument yesterday about upset stomach.

Dr. NOVITCH. It will settle a lot of things.

Dr. ———. If Alka-Seltzer were manufactured by some small company in Newark, New Jersey, and had a market of 150,000 a year, would the FDA be worried about litigation?

Dr. NOVITCH. That's an unfair question. Big or small, all alike.

Dr. ———. I think consideration here is that this will lead to litigation and Alka-Seltzer will have a very strong case that it is an antacid and that it is effective and safe when the two conditions exist. I wonder if consideration should be given to the question of secondary claims, that the antacid claim should not be a primary claim but could only be used as a secondary claim. Is that realistic?

Mr. YINGLING. That gets back to what Dr. ——— was saying, headache with—that's what I was asking before when you were talking about heartburn. It's definitely not a word that you would put with this type of combination, whether there was some type of labeling with this type of claim that you would approve.

Dr. ———. I would approve a cautionary statement on the labeling which said "should not be used for heartburn alone." How would that be? In other words, I'm willing to accept the fact that patients take Alka-Seltzer and they take it for all kinds of things, that their claims show that people take it in very small amounts most of the time, but .1 percent of the population takes more than five a day—.1 percent of the users take more than five a day, and I'd be willing to settle for something that said we will accept all that and put on the label that it should not be used for heartburn alone. How would you people feel about that?

Dr. ———. Or the other permitted antacid claims.

Dr. NOVITCH. Why not turn it around and instead of "not for heartburn alone," make the labeling cautionary enough so that anyone using it knows that is indicated only for the simultaneous presence of the GI and the analgesic related complaints, and make it stronger on the indications side.

Dr. ———. How would you phrase it?

Dr. NOVITCH. "To be used only when"——

Dr. ———. "When your heartburn is accompanied by headache?"

Dr. NOVITCH. Yes, or "only when your stomach complaints"—or however the layman refers to GI complaints—"for use only when acid indigestion, heartburn or sour stomach is accompanied by headache."

Dr. ———. Only when headache is accompanied by.

Dr. NOVITCH. Right. Only when headache is accompanied by these.

Dr. ———. Do we want to just say headache, only when headache——

Dr. NOVITCH. Or pain, as accompanied by pain.

Mr. YINGLING. Why don't you put "only when (analgesic claims) are accompanied by"——

Dr. ———. That won't do it because that means you can't use it for headache unless you have heartburn.

Mr. YINGLING. I really think, to put it in the warning not to be used as an antacid alone——

Dr. ———. Should not be used for simple heartburn.

Dr. ———. Then we would leave it the way it states, only after the words "antacid effects alone" say the label should contain a specific warning on this.

Dr. ———. The Panel is concerned about the indiscriminate use of aspirin combined with this other thing by persons with heartburn alone and feel that the label should—I think we should reflect some of our concern about this. Our concern is not with the product or its formulation, but simply with the fact that many people take it for heartburn alone and we don't see how the aspirin does anything except add harm. We don't believe it relieves the pain in the tummy and those statements should reflect that feeling.

Dr. ———. If we add those statements after the word "alone," would you be happy?

Dr. ———. I'd be happy.

Dr. ———. Well, I think I would make it a little stronger. I think at the top I'd say "should be marketed and labeled."

Dr. ———. That's what he said. We're going to work on this statement.

Dr. ———. Okay.

Dr. ———. Then what would happen would be we would add that after the word "alone," and then say comment and——

Dr. ———. Would you like to take a straw vote and see how many people won't accept it that way?

Dr. ———. Okay, we will, but I wanted to specify what we're talking about. How many people will accept it that way? Two.

Dr. ———. I'm not sure exactly how you're going to word it.

Dr. ———. We're going to say that the label should clearly contain a warning that it's not to be used for the three antacid indications alone.

Dr. ———. Yes, I'd accept that.

Dr. ———. I don't like it. I don't think there's any rationale for use of this to support that.

Dr. ———. How many people vote for using such a statement? Four. How many against it? Two.

Dr. ———. You're against it to make it stronger or weaker?

Dr. ———. I don't think the word "antacid" should appear here. I think people will use it as an antacid just as they are now. I think it's a fine buffered aspirin and I think it should be marketed as a buffered aspirin and let them make their own formulation without aspirin, and they will do very well at it. I don't think we should concern ourselves with the litigation problem. They might win. As ——— said, they could certainly make a good case.

(Discussion off the record)

Dr. ———. We're right in the sensitive area about whether a product like Alka-Seltzer should be permitted at all as an antacid or, as we had it originally, as an antacid if the patient has both a headache or a pain and an appropriate condition requiring it, and the Panel is quite divided right now. Some people feel strongly that the aspirin combination with an antacid should not be marketed or promoted for antacid purposes under any conditions. I think ——— has a point but I think it's sort of a side point.

Dr. ———. Well, I may be overridden by what you're talking about. I'm certainly willing to concede that, but I think on the other hand, we have to live with ourselves on this and I think if we really feel this way, then win or lose I think we have to go on record for what we think is correct.

Ms. ———. In terms of having a weak case, I think Dr. ——— just indicated that you didn't have a weak case, that you had lots of case experience that you could use to back this up.

Dr. ———. It isn't collected or available. That's the problem. It's anecdotal. What we need to be done is a prospective study.

Dr. ———. All they are talking about is they haven't received any more letters than this.

Dr. ———. That argument yesterday was full of holes. There were 12 places to attack to tear it down fairly rapidly.

Dr. ———. If you surveyed the AGA membership, how many people in the AGA would espouse the idea that it was good to add aspirin to an antacid? That's where it's at.

Dr. ———. Yes. It's just as rational to put something else in it.

Dr. ———. Again, shall I take a straw vote about the other version which just said "are not properly labeled or marketed for their antacid effects"? Do you favor that?

Dr. ———. Yes.

Dr. ———. Who's in favor of such a statement over one which would definitely exclude the marketing or labeling of this for antacid under any conditions? Three. Not you, ———?

Dr. ———. Well, I have to raise my hand, I guess.

Dr. ———. Well, you have been arguing for that.

Dr. ———. I'm suddenly confused. I wanted the statement to reflect our enormous concern with the addition of aspirin.

Dr. ———. But people didn't think that was strong enough. There was a split vote on that.

Dr. ———. I can't go home and say we took out anticholinergics and everything else in the book, but we left in aspirin.

Dr. ———. But what was wrong with the statement we had a little while ago?

Dr. ———. That was merely a warning that it shouldn't be used alone.

Dr. ———. Right. Then I'll go along with this.

Dr. ———. This will be on the inside of the box.

Dr. ———. Will you show me the hands again? Four. How many people against it? Two. I'm sort of on the fence on this one.

Mr. HUTT. That's an inaccurate statement. That goes on the outside of the box.

Dr. ———. I'm certainly in favor of the intent.

Dr. ———. Well, would you like to talk? We have been hung on many problems today. This is only one of them.

Mr. HUTT. I understand that. On this specific issue, my only comment would be if we're going to take Alka-Seltzer off the market, we've got to have damned good scientific data on which to base that decision because I'll get blown right out of court. It won't even be funny. I have no quarrel with whatever your decision is, but you have got to document it and document it in detail with case histories or scientific evidence of some kind that a product of this nature has proved to be harmful, because I can just tell you that it is going to be very difficult to convince the courts—and that is where my bag is, let's face it—that a product of that type is dangerous or harmful or should in any event not be on the market.

I'm willing to do it, obviously, if we've got the evidence to back us up. I obviously haven't the vaguest idea whether it should or shouldn't be on the market, and that's in no way my function.

Dr. ———. We're not saying it shouldn't be on the market. We're saying it should be on the market and any one of us would be willing to appear on television testifying to its virtues as an aspirin, but we are saying that our informed belief leads us to feel that it shouldn't be marketed as an antacid.

Mr. HUTT. But is it wrong to be marketed for use with both symptoms? That's the issue, as I understand it.

Dr. ———. We suggested earlier that we would be satisfied with a statement on the label that said "Do not use for simple heartburn or heartburn alone." Could you get that through the courts?

Mr. HUTT. I would say I would have no difficulty with that at all. As I understood the question—maybe I misunderstood—but as I understood the question was whether it would be required to have the concurrent symptoms and that simple antacid use alone would be prohibited. Now, I have no difficulty sustaining that in light of the inclusion of aspirin I would say I would have no problem.

Dr. ———. That's really where I'm at.

Dr. ———. But even the data there is real shakey.

Mr. HUTT. But what you voted on is that that product should not be on the market with any antacid claim and therefore the concurrent symptoms are just out. That's what you just voted.

Dr. ———. That's right. ——— shifts back and forth.

Dr. ———. What I really want is my original statement. If I can't get that———

Mr. HUTT. I didn't say you can't get it. Please don't misinterpret me. I said if we are going to take a product off the market of this length of use and do it on the grounds of lack of safety, we've got to have something to base it on.

Dr. ———. My original statement was I would like to have the statement reflect our concern about the addition of aspirin to the antacid and I'd like to have the label state "Do not use as an antacid alone. Do not use for heartburn alone." I'd be satisfied with that and not go any further.

Dr. ———. But could we go to that point? You feel you could win there, but I would question that, because the data is lacking there, too.

Mr. HUTT. I'll tell you why that would be, in my judgment a very simple issue; because there you have an ingredient, aspirin, which clearly is not effective or useful in terms of a condition like upset stomach or whatever it is that—acid

indigestion—I don't know what terms you're going to use—but whatever it is that the problem is in the stomach, aspirin isn't going to help it. Therefore, it would be wholly inappropriate to recommend it for use solely as an antacid. I don't think there would be anybody that could oppose that and I could win that hands down in any court.

Dr. ———. Except they argue that there are gastro-intestinal discomfort here that the aspirin is useful for. It isn't the headache.

Mr. HUTT. I hate to predict what any company is going to do, but I don't believe they would ever try to challenge it. If they did, I'd say it would be an open and shut case. I really feel that way.

The other, to me, is quite a bit different, and as I say, I'm perfectly willing to go to court on the basis of some good evidence.

Dr. ———. Suppose this were an anticholinergic. You probably feel you would not win it in that situation. You can't make that argument that it has no effect and you can't really show in the dose in that package that it's harmful. Your case then would be intrinsically weaker than with aspirin. Is that the type of thing you're saying?

Dr. ———. Except the ingredient has to be able to contribute.

Mr. HUTT. Yes. Does it contribute? Now, are you talking about a combination? What is the anticholinergic used for?

Dr. ———. They would say heartburn. It could have effects on gastric secretion.

Mr. HUTT. That's quite a different situation. There you're talking about another ingredient that is arguably or not arguably an antacid ingredient also. There the issue is whether it makes an antacid contribution. Here we're talking about something that is extraneous to antacid use.

Dr. ———. We're saying the same thing. Your case would be——

Dr. ———. I'm trying to write it out.

Mr. HUTT. Once again, I don't think that I should get into the scientific issue at all. Your scientific judgment has got to prevail. But whatever your judgment is—and this goes to a number of your decisions—it's got to be based on some data, some evidence, because one thing I have discovered in the courts is you can't go in and say, "Well, we think it's that way and you will just have to take our advice." We were just thrown out of court in Boston on the labeling of the Orinase, where 120 doctors challenged our labeling, as I'm sure you're aware of the case up there, and thus far have gotten us enjoined on the basis of the UGDP—we had proposed new labeling on the UGDP study. So we've got to have something to go on.

If you've got it, fine. Let's get it down and we'll go straight ahead.

Dr. ———. I don't think we have it at all.

Dr. ———. We'll go back now to the other one. The statement would read as it reads now, but after the word "alone" possibly something like this: "The label should clearly indicate that such a combination should not be used for the treatment of heartburn, acid indigestion and sour stomach unless these symptoms are accompanied by indications for an analgesic."

Mr. HUTT. Do you want a label warning ?

Dr. ———. Yes.

Mr. HUTT. Fine. I think we ought to write out the warning.

Dr. ———. That's it.

Dr. ———. You mean it should be called warning.

Mr. HUTT. We'd better work on it because I think we want to get it down and make sure everybody agrees that it's strong enough. You obviously do want to make it a strong warning and I think we ought to make it very strong—or is this in the nature of a caution?

Mr. YINGLING. I think it's in the nature of a warning.

Dr. ———. I think it's as dangerous as smoking cigarettes.

Dr. ———. Well the label should include a warning that such a combination——

Mr. HUTT. We want two things, I assume. One, we want the identity of the product to say analgesic and antacid. It has to have something up there. Now, do you want this warning pulled out from the usual warnings and put up close to the brand name? I would assume you might feel strong enough to do something like that.

Dr. ———. That's fine.

Dr. ———. I think it's such an established product that we probably do. If people continue to use it they won't see it otherwise.

Mr. HUTT. These are the kinds of considerations—again, I think you ought to go through the possibilities; where you want it placed; what the warning should say; should it be called warning or caution or special consideration,——?

Dr. ———. Warning.

Dr. ———. I think we all agree on warning. Well, we don't have to specify exactly where to put it. We want a prominent warning, prominently displayed warning.

Dr. ———. Do you feel such a warning should be backed up by evidence as well?

Mr. HUTT. A warning requires an awful lot less evidence. A warning really says there's not necessarily a cause and effect relationship, but until it's been disproved you shouldn't take any chances.

Dr. ———. Sometimes it has as much impact.

Mr. HUTT. But the fact is you frequently put on warnings where there's no proven cause and effect relationship, as you know. In fact, if there were a cause and effect relationship the next step from the warning is a contraindication.

Dr. ———. Now, may we have a vote of the Panel so we make this the final vote?

Dr. ———. Just one other question. Supposing Alka-Seltzer goes away and does studies over the next two years to show that in fact aspirin in duodenal patients is harmless and may be useful. Then that warning could be removed?

Mr. HUTT. That's right, and there's a procedure whereby they would petition us to change the monograph.

Dr. ———. Are you ready for a vote? It would say after the word "alone," "The label should include a prominently displayed warning that such a combination should not be used for the treatment of heartburn, acid indigestion and sour stomach unless these symptoms are accompanied by indication for an analgesic." It doesn't have to be exactly those words, but the sense.

All those in favor of this version, raise your hand. Six. All opposed? One.

Dr. ———. And record that the reason one is opposed is because he's plugging for elimination of any antacid claim so that in a sense also backs up this.

Dr. ———. It makes our position a little stronger.

Dr. ———. There's a citation I'd like to add to the ones in this section.

Dr. ———. Have you got it written out?

Dr. ———. I can just hand it to him. This is one showing what ——— mentioned before, that Alka-Seltzer is a frequently used analgesic in patients who have had major gastro-intestinal hemorrhage. May we insert that in the citations?

Dr. ———. That's the kind of data that you want to use. If this is available, I don't understand why——

Mr. HUTT. I agree with you, if it's available. Could I make one suggestion that might alleviate some of your problems? The Panel might wish to recommend further studies of a very specific nature, at which point the warning could either be removed or the indication could be removed, because if you leave it at this point nobody is going to know, certainly in the FDA, what studies you think would be appropriate to resolve whatever issue there is.

Now, apparently they came in yesterday with data. I haven't the remotest idea what their data showed or whether it was good, bad or indifferent, but if those data were felt to be inadequate to show whatever it was that you wanted shown, I would suggest that we somewhere just include a sentence in this that the Panel feels that additional tests should be run of the following nature to clarify some of these issues, and then just describe them in a general way.

Dr. ———. We haven't done that anywhere else, though.

Dr. ———. Furthermore, the problem is basically that it's just not rational, irrespective of any tests, to add an aspirin to an antacid. That's basically wrong.

Dr. ———. That's the issue.

Dr. ———. Nobody, if they started out—in spite of what ——— said—if they started out to make an ideal antacid, nobody would add aspirin to it, because it's damaging as an antacid. So the only test they could do would be to show out of 1,000 users nobody seemed to have any bad effects. But that's a hard thing to prove. I'm not sure that any additional studies would help very much.

Mr. HUTT. Well, I guess, if that's true——

Dr. ———. Would the Panel agree with that?

Dr. ———. Yes.

Dr. ———. I could see where a study—you said you have a number of cases and you have a number of cases and you have a number of cases and they're not on the record. Supposing the FDA then set up some sort of a polling of all gastroenterologists and other physicians about the incidence of complications where there was bleeding from using this. Then you would have a body of data with which you could counteract in low order anecdotal crap they get.

Dr. ———. May I suggest that you include that statement in this first sentence, that it is irrational? It concludes that fixed aspirin-antacid combinations are irrational for antacid use.

Mr. Hutt. For antacid use alone?

Dr. ———. Yes.

Mr. Hutt. There's no problem with that.

Dr. ———. That's really the basic issue. They are mislabeled because it's irrational.

Dr. ———. Antacid combinations are irrational for antacid use alone and therefore are not properly labeled or marketed for such effects. Leave out the "properly." Just say "should not be labeled or marketed for such use." We're trying to make it as strong as possible.

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Dr. ———. All right.

Dr. ———. Pepsin?

Dr. ———. Pectin is III. Pepsin is II.

Dr. ———. Phenacetin?

Dr. ———. II.

Dr. ———. I'm not clear on these analgesics. Why are they in II, if we're not totally disallowing Alka-Seltzer?

Dr. ———. We are. We're talking about antacids. We are disallowing it.

Dr. ———. We do have a problem.

Dr. ———. We've got a big problem.

Dr. ———. Back to the conceptual problem.

Dr. ———. Define the problem again.

Dr. ———. We're saying these things are not antacids under any circumstances. We're saying later on, if somebody happens to have both conditions it's all right to mix an antacid with something which happens to be aspirin.

Dr. ———. All right. So they're not antacids or correctives for antacids. That's the way we're classifying them now.

Dr. ———. In effect, you need a parallel list: the potential antacids and then the potential correctives, and one may not appear on one and maybe two on one and one on another. Is that right?

Mr. Fountain. The panel had under consideration at the time Mr. Hutt visited them, the antacid-non-antacid ingredients combinations, one of which is, of course, Alka-Seltzer. Mr. Yingling said at pages 25 and 26 of the transcript, and I quote:

> I think this is one area that we discussed before. Mr. Hutt would come in around ten o'clock and since we're spending a lot of time, why don't we cross this one off and let him discuss at that time some of the needs and the agency's problems and possibly even draw up an opening type of statement that we could make use of, if that would be acceptable with you.

The chairman responded: "Anything to get us out of this dilemma."

The question of the possibility of litigation concerning Alka-Seltzer was again raised. At page 58 one panel member asked: "If Alka-Seltzer was manufactured by some small company in Newark, N.J., and had a market of 150,000 a year, would the FDA be worried about litigation?"

To which Dr. Novitch replied: "That's an unfair question. Big or small, all alike."

This was followed by a discussion of how to modify the panel's position to reduce the likelihood of litigation. At page 58 a member suggested: "I wonder if consideration should be given to the question of secondary claims, that the antacid claim should not be a primary

claim but could only be used as a secondary claim. Is that realistic?"

Mr. Yingling replied: "That gets back to what Dr. ——— was saying, headache with—that's what I was asking before when you were talking about heartburn. It's definitely not a word that you would put with this type of combination, whether there was some type of labeling with this type of claim that you would approve."

It is obvious, at least it is to me, that FDA's concern with a court contest had quite an impact upon the panel. You might say that it had infected them. They were seeking ways of coming up with positions which would diminish the likelihood of contests.

Dr. Schmidt, the antacid panel was composed of scientific and medical experts, not attorneys, even though I can see the necessity for occasionally getting the advice of an attorney in certain areas.

Of what relevance to them is the question of possible litigation and how does the question of possible litigation change the scientific and the medical facts?

Dr. Schmidt. The panel was discussing the indications. Their charge included the proper labeling; that is, conditions for safe use. They were debating things like what words should be put on the label.

These are not chemical formulas and they are not things that have to do with toxicological, statistical kinds of things. The panel was very concerned when they were debating the difference between upset stomach and sour stomach and acid indigestion and gastric indigestion. These words are the scientific things the panel were discussing.

They were anxious that the background, the use of these terms, and the possible implications of their report be understood by them. They asked many, many questions about this. We did our best to answer them in a straightforward and truthful manner.

The words, we realized, would have to stand or fall on the scientific basis of them. For example, one of the questions they had to take up was whether or not there was scientific data which showed that acid indigestion really was associated with hyperacidity.

The same kinds of questions had to arise as to whether or not, say, there was a measurement scientifically in "sour stomach." These were the kinds of things they were discussing, whether or not these indications could be put on the label.

Mr. Chairman, in some respects these are issues they felt they had to understand as to the legal basis, and thus all of these questions, perfectly straightforward, perfectly legitimate, perfectly understandable.

Mr. Fountain. I can understand how they might be interested in expressing in an appropriate way their scientific evaluation and conclusions and recommendations, and knowing how some lawyers sometimes can take certain language which might be used and twist it around during the course of a trial, I can understand that. However, I just cannot see how the question of possible litigation could change the scientific and medical facts.

Mr. Hutt. No, Mr. Chairman. This is terribly important. Again, I have discussed it with many panels. Where there is general scientific agreement and no particular people appear before a panel to dispute that and no data are submitted to dispute it, then the need for the documentation is much less than where there is a major issue, a major controversy which is likely to result in major litigation.

I think any lawyer, and you yourself would agree, when you are preparing for litigation or preparing a case, if you know it is going to litigation you spend a great deal more time preparing than if you know it is not going to be disputed. This is simply the way any trial attorney would work.

Again I come back to what I mentioned to Ms. Jordan. I had to inform these scientists that for the first time they were in a regulatory system, not just a scientific system. That was a terribly important difference, something which they were not at all accustomed to.

Mr. FOUNTAIN. Nonetheless, you did not ask them for legal opinions. You asked them for scientific reasons.

Mr. HUTT. I asked them for legally supportable scientific opinions, yes.

Mr. FOUNTAIN. Legally supportable scientific opinions?

Mr. HUTT. Absolutely. If they are not legally supportable, if they used improper procedure, as on a couple of occasions there was a possibility of happening, or if they simply give a scientific opinion totally unsupported by the kind of evidence which would be necessary to uphold it in a court, then obviously it would be useless.

Mr. FOUNTAIN. How would the court know that? The minutes do not disclose any of what you are now saying.

Mr. HUTT. What is that?

Mr. FOUNTAIN. The minutes.

Mr. HUTT. How would the record show what?

Mr. FOUNTAIN. How would a court know what you are now telling us?

Mr. HUTT. The document has the scientific support in it.

Mr. FOUNTAIN. You say when you appoint them you tell them that they are supposed to come up with conclusions and recommendations that are legally supportable in court?

Mr. HUTT. Absolutely. If they were to use improper procedure that would——

Mr. FOUNTAIN. I am not talking about improper procedure.

Mr. HUTT. They would not be supportable legally.

Mr. FOUNTAIN. I am talking about the scientific facts and the truth, such that you say you cannot support in court. Are you saying they should not submit those facts if this is revealed to them——

Mr. HUTT. What you are saying is absolutely impossible. If they are the facts and the truth and scientifically supportable then it is legally supportable.

Mr. FOUNTAIN. I imagine that is a question of the way the law is written.

Mr. DRINAN. You are putting a gloss on the basic Commission. The Federal Register of April 5, 1973, states that a proposed review of the safety, effectiveness, and labeling is given to this independent advisory review panel. You have five M.D.'s and two Ph. D's. For you to insist they turn up with legally supportable conclusions, it seems to me, is an affront to the scientific panel.

Mr. HUTT. Father Drinan, again perhaps we are using different terminology to try to say the same thing.

What I mean is that the scientific data and the scientific reasoning must be set out in such a way that it can be enforced in the courts.

I do not think that anyone on this subcommittee would dispute that.

Mr. DRINAN. I dispute that. That is not up to you to say what is legally supportable. You are the executive branch. You should say:

Here is a group of experts in whom apparently we have faith and the Commissioner has faith. They have all types of credentials. They should call it as they see it.

If some said Alka-Seltzer is useless, as some would have, they should have been allowed to say that openly——

Mr. HUTT. They were allowed to say that.

Mr. DRINAN. Except that might not be legally supportable.

Mr. HUTT. You can't——

Mr. DRINAN. Wait. You can't have it both ways. You are saying it has to be legally supportable. If I were an M.D. or Ph. D., I would ask whether it is legally supportable. You are putting an inhibition to every conclusion they might arrive at.

Mr. HUTT. I disagree.

Dr. SCHMIDT. If someone comes to me, as some individual did, and said, "I hate aspirin," and then he quit, and that is all he said, and this was the basis of the report to me, it would be useless.

Mr. DRINAN. I would say you appointed the wrong guy.

Mr. HUTT. It would be legally unsupportable.

Dr. SCHMIDT. We are talking about legally unsupportable.

I go back and say, "You tell me why you hate aspirin. Give me the scientific reasons that you hate aspirin." That is what we are talking about.

In some instances we got expressions of opinion like you just gave. "It is my opinion that Alka-Seltzer," you said, "was worthless."

Fine. That is meaningless to me. I have to say, "Why do you feel Alka-Seltzer is worthless?" I say, "You must tell me why. Then I can have a legitimate basis on which to take action. This is a legal action. We are a legal regulatory agency and our actions must be supportable in a court of law."

I cannot go to the court of law with your opinions.

Mr. DRINAN. You have no right to insert the law at that stage at all. You have to say to them, "We want a scientifically supportable conclusion."

Dr. SCHMIDT. That is what we say.

Mr. DRINAN. No, you don't.

Dr. SCHMIDT. I have said all along——

Mr. DRINAN. Legally supportable. I have that term time and time again.

Dr. SCHMIDT. What is legally supportable is a scientifically supported argument.

When Mr. Hutt goes to them he says, "You cannot say just that you don't like this drug. If you give me the full scientific basis for your opinion, then that is legally supportable."

Mr. HUTT. That is what I have said.

Mr. FOUNTAIN. I think the record goes further than that. I think Father Drinan expressed it a while ago.

I will state it in a little different way. It seems to me that by raising and stressing the possibility of litigation to the point of permeating

the panel's discussion of all the claims they felt to be questionable, FDA might not have been promoting objective and dispassionate evaluation of scientific and medical facts.

Can you comment on that?

Dr. SCHMIDT. I object thoroughly to the implication of "comment." You have taken out of 3 days of scientific discussion, and so on, isolated paragraphs. All we have been talking about——

Mr. FOUNTAIN. It is not only 3 days.

Dr. SCHMIDT. We have been talking about one small issue on which there was a lot of talk regarding legal implications. However, these panels meet hour after hour and day after day. The kinds of discussions which have occupied our last 2 hours are a minority in those panel meetings.

Mr. FOUNTAIN. Anyway, let's continue.

At page 62 of the December 9 verbatim transcript, a discussion off the record occurred. Of course, we have no way of knowing what was said, but the chairman summed it up as follows:

> We're right in the sensitive area about whether a product like Alka-Seltzer should be permitted at all as an antacid or, as we had it originally, as an antacid if the patient has both a headache or a pain and an appropriate condition requiring it, and the panel is quite divided right now: Some people feel strongly that the aspirin combination with an antacid should not be marketed or promoted for antacid purposes under any conditions.

The transcript reveals, certainly, the panel's confusion. The panel members go round and round. There are questions again, and at page 64 of the December 9 meeting a panel member states:

> I'm suddenly confused. I wanted the statement to reflect our enormous concern with the addition of aspirin.

The chairman replied:

> But people didn't think that was strong enough. There was a split vote on that.

A third member of the panel joined in and said:

> I can't go home and say we took out anticholinergics and everything else in the book, but we left in aspirin.

Mr. Hutt, the transcript at page 64 shows that you appeared at the meeting. The chairman greeted you with:

> Well, would you like to talk? We have been hung on many problems today. This is only one of them.

Now, Mr. Hutt, from your remarks after you entered the room it appears that you were under the impression that the panel had voted that Alka-Seltzer should not be on the market for use as an antacid or for use in treating concurrent symptoms of upset stomach and aches and pains. You said on pages 64 and 65:

> I understand that. On this specific issue, my only comment would be if we're going to take Alka-Seltzer off the market, we've got to have damned good scientific data on which to base that decision because I'll get blown right out of court. It won't even be funny. I have no quarrel with whatever your decision is——

Mr. HUTT. That's right.

Mr. FOUNTAIN [continuing].

> But you have got to document it and document it in detail with case histories or scientific evidence of some kind that a product of this nature has proved to be harmful, because I can just tell you that it's going to be very difficult to convince the courts—and that's where my bag is, let's face it—that a product of that type is dangerous or harmful or should in any event not be on the market.

I'm willing to do it, obviously, if we've got the evidence to back us up. I obviously haven't the vaguest idea whether it should or shouldn't be on the market, and that's in no way my function.

Mr. HUTT. Mr. Chairman, that is a good illustration of the way I have said it to every panel. I will back up any decision they wish to make as long as they give me the scientific evidence and the scientific reasoning behind it. I feel very strongly that that is my function; that is, to lay out the ground rules and then say, "You make the decision and I will back it up under those circumstances."

Mr. FOUNTAIN. A panel member replied:

We are not saying it shouldn't be on the market. We're saying it should be on the market and any one of us would be willing to appear on television testifying to its virtues as an aspirin, but we are saying that our informed belief leads us to feel that it shouldn't be marketed as an antacid.

You responded with these words:

But is it wrong to be marketed for use with both symptoms? That's the issue as I understand it.

Your question led a panel member to reply, at pages 65 and 66:

We suggested earlier that we would be satisfied with a statement on the label that said "Do not use for simple heartburn or heartburn alone." Could that get through the courts?

You responded in part:

I would say that I would have no difficulty with that at all.

In the discussion which followed, you gave further assurance that if the product was recommended for the concurrent analgesic and antacid effect, you would have no trouble in court, and this apparently had some influence upon the panel, for the chairman stated at page 69, or maybe you persuaded them:

We'll go back now to the other one. The statement would read as it reads now, but after the word "alone" possibly something like this: "The label should clearly indicate that such a combination should not be used for the treatment of heartburn, acid indigestion and sour stomach unless these symptoms are accompanied by indications for an analgesic."

Then there was discussion concerning the need for a warning, and in this connection at page 70 you told the panel:

We want two things, I assume. One, we want the identity of the product to say analgesic and antacid. It has to have something up there. Now, do you want this warning pulled out from the usual warnings and put up close to the brand name? I would assume you might feel strong enough to do something like that.

Mr. Hutt——

Mr. HUTT. Again, Mr. Chairman, this is a good illustration of how I frequently will probe the panel in order to clarify exactly what it is that they want done.

Mr. DRINAN. You said you frame the question.

Mr. HUTT. Yes, I was asking what they wanted. Because of the tone of the discussion, Father Drinan, it was unclear whether they wanted to leave the warning in the warning section or to make it more prominent. I said that I assumed from their discussion they wanted it more prominent.

Mr. FOUNTAIN. Just prior to your statement to the panel, they had had a long discussion and apparently had voted by majority vote that

the product should not be on the market with any antacid claim. In connection with that vote, you observed at page 66:

> And therefore the concurrent symptoms are just out. That's what you just voted.

After receiving assurances from you that if the labeling for Alka-Seltzer recommended concurrent antacid and analgesic use, you would find no difficulty winning in court, the panel apparently made an abrupt turnabout and approved such labeling.

Mr. HUTT. Mr. Chairman, I would first point out that when I came in, as the transcript says, which I must say I have never seen although I do recall the incident, I clearly stated that I was perfectly willing to defend any position they wanted to take, that indeed that was my function, as long as they laid out some kind of good sound scientific evidence and the reasoning behind it to document that position.

Mr. FOUNTAIN. In connection with your expression——

Mr. HUTT. Whatever position. I also said it was not my function to tell them what position to take.

Mr. DRINAN. Except you told them you would be blown out of the water——

Mr HUTT. Without scientific data, yes, sir. I did say that. I have said that to every panel and I have said that 20 times this morning.

Mr. DRINAN. You made it clear you didn't want to take on a ban of Alka-Seltzer unless it was based on something you had not seen. You framed the question, you loaded the issue, and you put it one way.

Mr. HUTT. I am sorry, but I disagree with you.

Mr. DRINAN. That is the issue.

Mr. HUTT. That is inaccurate. I said I did not know what the scientific data are. I have never seen the scientific data on Alka-Seltzer. I must confess I do not think that is my function.

Mr. MEZVINSKY. Wouldn't this have been disputed no matter what? You still have a court case staring you in the face no matter what?

Mr. HUTT. No, sir.

Mr. MEZVINSKY. Put it this way—no matter what the vote you still would probably have a court case. I can't understand the hesitancy. Are you asking that the panel act all together in one voice?

Mr. HUTT. No.

Mr. MEZVINSKY. You are bound to have a person who may differ with you.

Mr. HUTT. If I may please explain. The issue was that the panel was considering, as the chairman has pointed out, various different possible ways of handling it. What I said was I do not care what you do as long as you back up that final conclusion and recommendation—whether it is a split vote or unanimous vote is irrelevant—with good sound documentation in the scientific literature or whatever other kind of scientific evidence might be available, together with a sound discussion of the scientific rationale for your final recommendation.

I said either way you want to go or any of 17 other different ways you might want to go is acceptable to me as a lawyer, and I can defend it in court and will win in court if it meets that test. If it does not then I cannot prevail in court.

Mr. MEZVINSKY. Don't you think they are aware of that fact?

Mr. HUTT. No. Again, I come back to the discussion earlier today——

Mr. MEZVINSKY. Why are they meeting and making a decision? Is it simply a pro forma gathering of scientists?

I don't understand why you have to go through this whole procedure with them two or three times. They know what their decision is. I think they very well understand the significance of their decision once they have voted.

Mr. HUTT. Once again, these are people very accustomed to writing general scientific review articles and participating in the kind of general scientific discussion that goes on every day in medical circles. They have never before, any one of them, participated in a law enforcement project, which is what this was.

Mr. DRINAN. It is not that at all.

Mr. HUTT. I am sorry, it is a law enforcement project.

[An exchange of correspondence between Chairman Fountain and Mr. Hutt on this subject follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
OFFICE OF THE SECRETARY,
Rockville, Md., May 17, 1975.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: During the course of the recent hearing on the OTC drug review, members of the Subcommittee expressed concern about my insistence upon scientific documentation and justification for the conclusions and recommendations of each OTC drug review panel. I stated at the time, and wish to reiterate, that this is necessary to make the panel reports legally defensible, and that the Food and Drug Administration would not be willing to accept reports that are not legally defensible.

Because I was not aware that this would be an issue at the hearing, I did not bring with me at the time examples of the case law which fully support my position. Accordingly, I am requesting that this letter be included in the printed record of the hearing at the point where the discussion took place.

In *Securities & Exchange Comm'n* v. *Chenery Corp.*, 318 U.S. 80, 87 (1943), the Supreme Court stated that "The grounds upon which an administrative order must be judged are those upon which the record discloses that its action was based." In that case, the Supreme Court reversed the SEC's order because "the considerations urged here in support of the Commission's order were not those upon which its action was based," and remanded the case because "the orderly functioning of the process of review requires that the grounds upon which the administrative agency acted be clearly disclosed and adequately sustained." *Id.* at 91, 94.

In *Investment Co. Institute* v. *Camp*, 401 U.S. 617, 628 (1971), the Supreme Court similarly stated that "Congress has delegated to the administrative official and not to appellate counsel the responsibility for elaborating and enforcing statutory commands." See also *Federal Trade Commission* v. *Sperry & Hutchinson Co.*, 405 U.S. 233, 245–250 (1972), and the cases cited therein.

The Administrative Procedure Act, 5 U.S.C. 553(c), requires that an agency incorporate in each regulation it promulgates "a concise general statement" of the basis and purpose of the regulation. The courts have held that, although an agency is not required to develop specific and detailed findings and conclusions of the kind customarily associated with formal proceedings, it does require a sufficiently reasoned articulation of the administrative decision to permit meaningful judicial review.

In *Automotive Parts & Accessories Ass'n* v. *Boyd*, 407 F. 2d 330, 338 (D.C. Cir. 1968), the court emphasized that the statutory terms "concise" and "general" should not be read in an overly literal way. The court stated that it would require sufficient discussion to "enable us to see what major issues of policy were ventilated by the informal proceedings and why the agency reacted to them as it did."

In *Environmental Defense Fund, Inc.* v. *Ruckelshaus*, 439 F. 2d 584, 597–598 (D.C. Cir. 1971), the court stated that "We stand on the threshold of a new era in the history of the long and fruitful collaboration of administrative agencies and reviewing courts," and that "Courts should require administrative officers to articulate the standards and principles that govern their discretionary decisions in as much detail as possible." It concluded that "Discretionary decisions should more often be supported with findings of fact and reasoned opinions" thereby "enhancing the integrity of the administrative process." Since then, the courts have required substantial explication of the basis for any administrative decision.

Examples of the close judicial scrutiny over agency justification of its decisions may be found in two recent Food and Drug Administration cases. In *Cooper Laboratories, Inc.* v. *Commissioner, Food and Drug Administration*, 501 F.2d 772 (D.C. Cir. 1974), the court upheld the agency's summary judgment withdrawing approval of a new drug application by a 2–1 vote. The majority nonetheless felt constrained to add a caveat at pages 786–787, stating that "we are not pleased with the draftsmanship displayed in the instant order" and that "we shall expect the FDA to make its criticisms express and detailed, and to cite precisely to the pertinent regulations and evidentiary flaws" in future orders of this type. The court stated that such orders must "make utterly transparent why each piece of submitted evidence fails the particular regulatory provisions relied upon" and that "the Administration must explain and defend its chosen interpretation." The dissent went one step further and contended that, because the order did not cite the scientific documentation and justification in sufficient detail, the entire matter should have been remanded for an administrative hearing.

Similarly, in *National Nutritional Foods Ass'n* v. *Weinburger*, ——F.2d—— (2d Cir. 1975), the court upheld the agency's legal authority to establish binding substantive regulations requiring that vitamins A and D be sold on prescription, but remanded the matter to the District Court for the agency more adequately to explain the reasons for its decision. The court pointed out that the Food and Drug Administration is obligated "to publish a statement of reasons that will be sufficiently detailed to permit judicial review," and that "agency action will not be upheld where inadequacy of explanation frustrates review." It required that the agency provide "a thorough and comprehensible statement of the reasons for its decision" and therefore remanded the case to the District Court for a hearing at which the basis for the agency's decision could be more thoroughly presented.

Finally, the courts have recently made it clear that judicial review will be based solely upon the administrative record before the agency when the decision was made, and the rationale and justification given for the decision at that time. See, e.g., *Camp* v. *Pitts*, 411 U.S. 138 (1973); *Citizens to Preserve Overton Park, Inc.* v. *Volpe*, 401 U.S. 402, 419–420 (1971); and *Bradley* v. *Weinberger*, 483 F.2d 410, 414–415 (1st Cir. 1973).

Accordingly, it would be irresponsible for the Food and Drug Administration not to insist upon both sound scientific documentation and substantial scientific explanation and justification for the recommendations made by the OTC drug review panels. Without such documentation and justification the results would be legally indefensible and pointless.

Sincerely yours,

PETER BARTON HUTT,
Chief Counsel,
Food and Drug Administration.

INTERGOVERNMENTAL RELATIONS AND
HUMAN RESOURCES SUBCOMMITTEE
OF THE COMMITTEE ON GOVERNMENT OPERATIONS,
Washington, D.C., May 21, 1975.

Dr. ALEXANDER M. SCHMIDT,
Commissioner, Food and Drug Administration
Rockville, Md.

DEAR DR. SCHMIDT: I have received a May 17, 1975 letter from Peter Barton Hutt in support of his position that panel reports must be legally supportable. Mr. Hutt's letter will be inserted into the hearing record.

As an attorney, I would assume that all agency *final orders* must be legally defensible. This, however, is quite a different matter from asking drug review panels to give their independent scientific and medical judgments, as experts

qualified by training and experience, after evaluating the available data. After receiving adequate instructions, the panel must be free to consider and evaluate the scientific evidence, unhampered by further expressions of agency policies and preferences, if they are to arrive at sound and independent scientific and medical judgments.

I believe it can be demonstrated from past FDA experience that a final order based on the best available scientific and medical knowledge and judgment will be sustainable in most courts of the Nation. Further, I do not believe that the degree of proof required to sustain a panel's conclusion that a given drug is not generally recognized as safe is in the same category as the proof required to support a finding that a drug is unsafe. Indeed, as brought out during the hearing, some courts have found in favor of the Government solely on the basis of an affidavit submitted by an FDA medical officer that a given drug was not generally recognized as safe—as occurred in the AMP case.

Sincerely,

L. H. FOUNTAIN,
Chairman.

Mr. FOUNTAIN. I don't know how far we can get this afternoon, but we will stand in recess until 1:30.

[Whereupon, at 12:15 p.m., the subcommittee recessed, to reconvene at 1:30 p.m., the same day.]

AFTERNOON SESSION

Mr. FOUNTAIN. The subcommittee will come to order. Let the record show that a quorum is present.

Mr. Hutt, getting back to your statement to the panel, the panel had had a long discussion and apparently had voted by majority vote that the product should not be on the market with any antacid claim. In connection with that vote, you observed at page 66, and I quote:

> And therefore the concurrent symptoms are just out. That's what you just voted.

After receiving assurances from you that if the labeling for Alka-Seltzer recommended concurrent antacid and analgesic use, you would find no difficulty winning in court, the panel apparently made an abrupt turnabout and approved such labeling.

Mr. HUTT. If I may interrupt, I think that is an inaccurate representation of what happened. It was after receiving assurances from me that I would be happy to support in court any position on which they would set out the scientific data and adequate scientific reasoning, it was after that assurance that they came to their final conclusion.

Mr. FOUNTAIN. I have no objection to your adding that as part of the total picture. Nevertheless, after whatever it was you did, they did turn about and change their opinion.

In connection with your expressed confidence in winning in court under such labeling, let me quote your statement at page 67 of the transcript:

> I don't think there would be anybody that could oppose that and I could win hands down in any court.

That is correct, is it not?

Mr. HUTT. That is correct. I am still of that opinion. It has not been challenged in court.

Mr. FOUNTAIN. Why are the minutes completely silent with respect to the doubts and state of confusion of the panel, as reflected in the

transcripts, and your strong statement to them that they would have to document their decision with detailed case histories or other scientific evidence that a product of this kind has proved to be harmful, and that their expert opinion based upon their knowledge, training, and experience was not enough to support court action?

Mr. HUTT. I am not sure that I said their expert opinion based upon such data would not be sufficient. I believe I said their expert opinion based upon data would be sufficient.

Mr. FOUNTAIN. Without the documentation.

Mr. HUTT. But it has to be based on something, Mr. Chairman. What I said was the same thing that we say to all our panels, namely, sheer opinion, just sheer, unadulterated and unsupported opinion, is not sufficient to justify any particular decision of any type. But, in any event, as to the question of why the minutes did not reflect that, I would assume it is because I say that all the time and it is not considered something which is worthy of reporting.

I always assumed that sheer, unsupported opinion is not sufficient to support any kind of Food and Drug Administration action. I doubt that that would appear in any minutes of any panels.

Mr. FOUNTAIN. Of course, the Advisory Committee Act does require detailed minutes.

Mr. HUTT. Yes, sir. As you have pointed out earlier, Mr. Chairman, that requirement is something of a subjective requirement. I do not believe the detailed minutes would require a statement of the kind that I made to be reflected.

Mr. FOUNTAIN. Did you understand that the members of the panel felt that they were not permitted to evaluate the scientific issues solely on the basis of scientific knowledge?

Mr. HUTT. Again I am not clear on what the question is. You said the basis of scientific knowledge. If that includes data and evidence, then I would say that they are entitled obviously to use that. If it includes unsubstantiated and unsupported opinion, then that would not be sufficient.

Mr. FOUNTAIN. Anyway, they were not permitted to evaluate the scientific issues on the basis of their scientific knowledge which they presented to you.

Mr. HUTT. I am sorry. I think that is an inaccurate statement, Mr. Chairman. What I said was——

Mr. FOUNTAIN. Were any opinions expressed by members that they were upset, annoyed, or distressed?

Mr. HUTT. I have not reviewed that transcript at all. All I can rely upon is my memory of what happened roughly 3 years ago, and I must confess I would have to review the transcript.

I do not off the top of my head recall that, Mr. Chairman.

I do recall receiving a copy of a letter from Dr. Ingelfinger subsequently in which he wrote either the Director of the Bureau of Drugs or the Commissioner stating that he was unhappy with the way that I had pressed the panel, literally on more than one occasion and in my discussions with him, in requiring that panel, like all other panels, to document whatever their decision was and to explain it.

He and I subsequently have had a good laugh about that, and after the process was all over he said to me, on more than one occasion, both at a press conference and subsequently, that that was the best

thing that ever happened to the panel, that he recognizes now that it is something different to write an article for the New England Journal of Medicine, which he edits, as you know, as contrasted with writing the kind of regulatory scientific report that is the subject of this OTC drug review.

I think if you were to ask him that he would no longer be quite as concerned with the vigor, admittedly, the vigor that I pressed him and the entire panel in terms of being specific in making recommendations.

Mr. FOUNTAIN. Did you observe that not only Dr. Ingelfinger but that other members of the panel felt that you were invading their province and interfering with their ability to make an effective decision?

Mr. HUTT. No; I did not feel that at the time, Mr. Chairman. It is entirely possible they might have felt that way, but I think there was an understanding of what I was driving at, that I did not care what their conclusions were as long as they stated them in a way that I could then go to a court and enforce.

Mr. FOUNTAIN. I am placing into the record a letter from Franz J. Ingelfinger, M.D., the panel's chairman, dated December 11, 1972, and addressed to Henry E. Simmons, M.D., Director of the Bureau of Drugs of FDA.

[The letter referred to follows:]

THE NEW ENGLAND JOURNAL OF MEDICINE,
Boston, Mass., December 11, 1972.

HENRY E. SIMMONS, M.D., M.P.H.
Director, Bureau of Drugs
Food and Drug Administration
Rockville, Md.

DEAR HENRY: I am so sorry I didn't have a chance to talk to you in addition Friday afternoon, but, as you recall, it was raining heavily and my only chance of getting back to the hotel with the group, it seemed to me, was to go with them. Furthermore things were getting late. It was practically 5:45 at that time.

I think we can settle the problem by correspondence, but it will require careful reading of the letters. There was some misunderstanding, I suspect, on your part.

I sent to you a statement that originated with Dr. Howard at the AMA (the Executive Vice President) but that reached me through the Massachusetts Medical Society. It stated categorically without qualification "Any physician who holds an investigational grant in the therapeutic category involved * * * will have to be excluded from consideration for panel membership". I doubted that statement because a number of our panel members are right now involved in investigation of the therapeutic categories involved.

You wrote "Any person must be excluded from panel membership if he is currently a paid investigator or currently holds an investigational grant in a therapeutic category involved or otherwise *has a relationship with a company* * * *". Of course company-related investigators are excluded. But the statement that was distributed by the AMA via its state affiliates is that *any* investigator is eliminated, including those that hold grants from the NIH. If that statement were true you certainly couldn't have appointed John Fordtran as a consultant.

The problem with the AMA statement is that it did not make clear that only company-related investigators were excluded. If the statement as distributed by the AMA were true, there wouldn't be a single member of the OTC antacid panel except myself.

Perhaps it would have been better that way, for we have had our troubles. In particular the necessity of twisting and distorting scientific facts to make it fit legal language requirements have proved almost insuperable. All this came out after the meeting on Friday with the Advisory Board. In particular the problem was emphasized by Peter Hutt's presentation Saturday morning. At one point several of the panel people were at the point of absolutely quitting saying they could not put their names to such distorted statements.

I think we are managing to create somewhat of a compromise although it will leave most of us unhappy. Somehow, it seems to me, the FDA and Congress itself must come to realize that to distort scientific fact to make it meet some legal language is not only unjustifiable but—to put it bluntly—stupid.

I myself was very discouraged on Saturday but, after my arrival home, picked up a bit in spirit. In fact, it is even possible that we may be able to finish the matter by mail and telephone. I shall certainly try, both for the sake of the FDA and for our sake.

Merry Christmas to you.

Sincerely yours,

FRANZ J. INGELFINGER, M.D.

Mr. FOUNTAIN. I will read pertinent parts of the letter as they relate to the panel's December 8 and 9, 1972, meeting, beginning with paragraph 1 of page 2.

Quoting from Dr. Ingelfinger's letter:

Perhaps it would have been better that way, for we have had our troubles. In particular the necessity of twisting and distorting scientific facts to make it fit legal language requirements have proved almost insuperable. All this came out after the meeting on Friday with the Advisory Board. In particular the problem was emphasized by Peter Hutt's presentation Saturday morning. At one point several of the panel people were at the point of absolutely quitting saying they could not put their names to such distorted statements.

I think we are managing to create somewhat of a compromise although it will leave most of us unhappy. Somehow, it seems to me, the FDA and Congress itself must come to realize that to distort scientific fact to make it meet some legal language is not only unjustifiable but—to put it bluntly—stupid.

I myself was very discouraged on Saturday but, after my arrival home, picked up a bit in spirit. In fact, it is even possible that we may be able to finish the matter by mail and telephone. I shall certainly try, both for the sake of the FDA and for our sake.

Mr. HUTT. Mr. Chairman, that letter is the one I had referred to. I was concerned about that because I do not think that what Dr. Ingelfinger said there is what you would interpret or someone who was not there would interpret as to what actually did happen.

When I talked to Dr. Ingelfinger subsequently, as I mentioned, about that, what it turned out he was concerned about was my insistence upon documentation, because I had not insisted, to the best of my recollection, in the entire discussion of any particular type of "legal" language.

What I was insisting upon was that there be good "scientific" language on which then for legal purposes we could rely.

I think it is relevant, and I would like to read just one paragraph of his subsequent speech which was delivered in July of 1973 before the American Pharmaceutical Association dealing with this precise issue, where he said:

Some of the critics of the report also managed to insert the innuendo, that the panel acted as a pawn of big business and that it was out to do in the consumer. Rubbish.

The panel's goal was to make recommendations that it thought would be of the greatest benefit to the public. It was not concerned with what was good for Miles Laboratory, nor, for that matter, with what was good for Ralph Nader.

The recommendation that affected Alka-Seltzer—which incidentally was just one portion of a lengthy report that took up many matters—was made in the belief that the public would not benefit if a well-buffered aspirin preparation were at the present either removed from the market or sharply restricted in its use.

And he goes on and discusses that. So at least at that time, and as I mentioned in his subsequent conversation with me, he recognized

that what happens to many panels, when they reach the end of the road and then are told by me, as I have to at times, that further work is still required, they get frustrated and irritated and a letter of that kind can result.

Mr. FOUNTAIN. Of course, we picked this particular part of the letter because we though it summarized what a full reading of the whole transcript indicated.

Mr. HUTT. I think it is quite inaccurate misrepresentation of the entire transcript, Mr. Chairman. I do not recall——

Mr. FOUNTAIN. You think this letter is?

Mr. HUTT. Yes. I do not recall any requirement or request on my behalf that they use any legalistic language at all.

I could be wrong, but if there is a part in the transcript I would like to have your reference to it where I made such a statement.

Mr. FOUNTAIN. This is Dr. Ingelfinger's statement on December 11, 2 days after——

Mr. HUTT. That is correct. As I said, he and the panel had come to that meeting thinking that the whole job was done and the report was not at that point sufficiently done and further work was needed.

[See appendix pp. 349–350 for submission by Mr. Hutt on this subject.]

Mr. FOUNTAIN. Notwithstanding the fact that during the course of that meeting you had met with the panel a number of times and explained to them what they were supposed to do.

Mr. HUTT. That is correct. Indeed, I think it is fair to say that the final report did not still explain some things in the detail that I had requested. I know that is certainly true of parts of other reports.

I seek, obviously, perfection. We do not get it, and that is not surprising. However, it seems to me that my job, on behalf of the agency and the public, is to get the best report out of every panel that can possibly be done. If I did not push them to the point where they got a little irritated at me, clearly I would not be doing my job.

Mr. DRINAN. Are you not a little disturbed, though, that a distinguished chairman of an outside advisory group such as this would even feel this way, that he would feel that the section of the Federal law I mentioned this morning had been violated?

He felt, apparently, there was an inappropriate influence by the appointing authority.

Comment on that, if you will.

Also, I find it a little astonishing that the general counsel of a big agency should spend so much time with a panel seeking to help their conclusion when the panel really doesn't deal with anything overwhelmingly important to the agency. There are other very important questions out there.

Why did you not, if you felt they should have a lawyer, why did you not assign just some lawyer who would help them? Why does the general counsel do this work which, frankly, is not that important?

Mr. HUTT. I will answer the second question first. I will return to the first part.

This dealt with 8,000 products, Father Drinan, 8,000 antacid products.

Mr. DRINAN. 200,000 OTC's.

Mr. HUTT. As I explained at the last hearing and hearing before, this represents in this one single report greater enforcement activity

than was undertaken in the entire history of the Federal Food, Drug, and Cosmetic Act from 1906 to the present against all over-the-counter drugs—all of any type. That was why it was so important.

Second, it was the first panel report. I have not spent as much time on subsequent panel reports. We had to work out some of the procedures, some of the methods of doing business, some of the approaches, with the first panel which would then be used for the next 16 panels.

Mr. DRINAN. What are the priorities by which this particular panel was first and so much time was spent on it when there are so many potentially far more dangerous products in other areas?

Mr. HUTT. There were basically two panels that were the first two panels. One was the antacid panel and the second was the antimicrobial I panel.

We wanted to take one of the most important issues first, namely, antimicrobial drugs. Hexachlorophene, which was a very serious problem, was involved in the antimicrobial I panel and antimicrobial drugs in general can have serious potential toxicity problems.

At the same time we wanted to have as one of the first panels one that would allow us, in a sense, to work out some of the bugs that would be relatively more easy to do, so that we could do it relatively quickly and establish a pattern that the other more difficult issues could then follow along in.

Now I would like to go back, if I may, to your first question. I was disturbed by that letter. That is the reason I did talk to Dr. Ingelfinger subsequently. If I had thought that I had unduly—and I emphasize unduly—influenced the panel in terms of substance it would be a very serious criticism.

I clearly influenced the panel in terms of telling them what is required for our purposes in terms of scientific documentation and scientific reasoning. I do not regard that as improper, and his criticism to the extent it is related to that I would regard as a misunderstanding on his part of the function of the panel.

Mr. DRINAN. What would you think of a statute enacted by the Congress to the effect that no administrative officer of any agency with an advisory committee of this kind could interfere or intervene in the deliberations of this independent outside advisory committee?

Mr. HUTT. I think it would be so much contrary to the public interest that you in effect would be doing away with advisory committees. It would destroy their usefulness to the agency, it would destroy their usefulness to the public.

Mr. FOUNTAIN. I missed the question.

Mr. DRINAN. I can restate it.

Suppose the Congress altered these regulations about advisory committees and stated that:

Strengthen this language. Not merely do we outlaw inappropriate influence by the appointing authority, but we outlaw any intervention or interference or involvement by the appointing authority in the work of the advisory committee.

Mr. Hutt gave his answer. If he wants to repeat it, he may.

Mr. FOUNTAIN. I heard the answer. I was not quite sure of the form of the question.

Dr. SCHMIDT. As I told your staff, I have a commitment later on this afternoon out of town. I have to make an airplane and I have to leave. For this I apologize.

I had not anticipated this session would continue into this afternoon.

I would like to make one or two statements before I leave. One is that when I became Commissioner clearly this OTC review was underway. The antacid panel had come to the promulgation of its report.

Because of the importance of this process I reviewed very, very carefully the procedure which had been set up and the functioning of the committees. I concluded that it was indeed appropriate and did safeguard the public interest. Indeed my opinion then, when I came in from the outside and looked at this process, was that it was the best kind of activity of its nature that I had ever seen in the Federal Government.

I am absolutely persuaded that this process of three public iterations through the promulgation of their report, the tentative monograph and the final monograph, for which I take full responsibility, is an absolutely sound process.

I would like to state very clearly that I, at this point, am responsible for this process. It has my absolute confidence.

Finally, when this three-iterative process is over, the final decisions are mine. What happened in regard to Alka-Seltzer, for example, was my decision.

If questions would come up about that I would hope that at the next session, by writing, or whatever, I might be able to state very clearly the reasons for the actions that I took.

[See p. 367 for September 2, 1975, letter from Commissioner Schmidt to Congressman Fountain.]

Mr. FOUNTAIN. We would be glad to give you another opportunity.

Right at this moment, inasmuch as you have to depart, we will take a recess in order to vote. After reconvening, we will try to finish up, as far as we can without Dr. Schmidt.

Mr. HUTT. That would be very helpful.

[A short recess was taken.]

Mr. FOUNTAIN. We were talking about objections of the panelists to the manner in which you participated in their deliberations.

Mr. HUTT. Yes, sir.

Mr. FOUNTAIN. Apparently your comments to the advisory committee were the subject of an objection from one or more members of the public. I base this on the fact that in the Federal Register, volume 39, No. 108, June 4, 1974, which contained your final order for antacid and antiflatulent products, at page 19871, which I am placing into the record, the following statements appear:

> One comment objected to comments made to the Antacid Panel by the Assistant General Counsel, Food and Drug Division, Department of HEW, and to the participation of the Assistant General Counsel in this matter because prior to his government employment he had provided legal advice to a client who had manufactured an antacid/analgesic combination drug.

[The material follows:]

[From the Federal Register, June 4, 1974]

> * * * physicians may approve or disapprove of a particular combination drug. Unsubstantiated opinion is no substitute for well-grounded scientific evidence. Sixth, the mail questionnaire focused upon a particular brand of a marketed product rather than upon a request for scientific evidence relating to a type of combination drug. This reference introduced further subjective factors into the response, relating to the labeling and advertising for the particular brand product mentioned, unrelated to the scientific and medical issues involved. Accordingly, the Commissioner concludes that this mail survey is entitled to little or no weight with respect to this matter.

69. One comment objected to comments made to the Antacid Panel by the Assistant General Counsel, Food and Drug Division, Department of HEW, and to the participation of the Assistant General Counsel in this matter because, prior to his government employment, he had provided legal advice to a client who had manufactured an antacid/analgesic combination drug.

The Commissioner has thoroughly reviewed this matter and has concluded that no impropriety has occurred. The Assistant General Counsel has stated that he had not advised the company involved on any of the issues involved in the OTC Review and that he has followed the guidelines for disqualification which he established in testimony before the Senate Committee on Commerce on September 17, 1971, which exceed the requirements of the law. A copy of that testimony has been included as part of the administrative record of this proceeding.

Moreover, the Commissioner reiterates that the decision on both the tentative final order and this final order with respect to the antacid/analgesic combination involves medical and scientific issues for which he is responsible, and not legal issues. The Commissioner advises that, in considering the status of the combination, his decision has been based upon sound scientific evidence and reasoning rather than upon theoretical possibilities, particularly in light of the long marketing history of this type of product without any significant reported safety problem. The criteria for a combination drug are established in § 330.10(a)(4)(iv) (formerly § 130.301(a)(4)(iv)) of the regulations in readily-understandable terms, and the Commissioner has applied those criteria as they are written. The Commissioner and his medical advisers have reviewed the administrative record in this proceeding, and the Commissioner personally presided over the public hearing at which the status of an analgesic/antacid combination drug was a major issue. Thus, full responsibility for the decision on this matter rests with the Commissioner, and not with the Assistant General Counsel, the Antacid Panel, or any other persons.

70. There was comment that the population to which the antacid/analgesic combination is directed contains a large number of individuals who are at an increased risk from salicylates because of underlying diseases. The comment conceded that an analgesic and antacid would be appropriate treatment for a person with hyperacidity and headache.

The Commissioner concurs with the comment that an antacid and an analgesic given concurrently would be the drugs of choice for a person with hyperacidity and headache. The Commissioner concludes that the data submitted support a fixed dosage combination for OTC use for this purpose and that in fact for many people the combination may be safer than taking the individual ingredients separately. There is some evidence that whatever harmful effect may result from salicylate may be reduced by buffering it with an antacid ingredient. Such a protective effect could not occur unless ingestion is at least simultaneous and may not occur without prior admixture. The Internal Analgesic Panel is considering appropriate labeling for analgesic ingredients, including whether warnings may be appropriate for salicylates to prevent use in situations where it could be harmful.

71. There was comment that, where there is inclusion of a salicylate, a warning statement concerning peptic ulcer would be appropriate on the antacid/analgesic combination.

The Commissioner will not comment on this issue at this time because the Internal Analgesic Panel is considering appropriate labeling for analgesic ingredients. As already noted above, the Commissioner will address this issue in the course of reviewing that Panel's recommendations.

72. There was comment that the finding that an antacid/analgesic combination is irrational for antacid use alone should not apply where sodium acetylsalicylate is used in a highly buffered solution.

This matter was fully considered in paragraph 64 of the preamble to the November tentative final order. To accept this comment would be to allow the use of a salicylate in a product that is represented only for antacid use. Until adequate and well-controlled studies are presented to show that a salicylate is effective for relief of upper gastrointestinal symptoms, it would be misleading for a product to represent that a salicylate is useful for relief of acid indigestion or other symptoms for which antacids are effective.

73. There was comment that data had been presented to show that sodium acetylsalicylate in a highly buffered solution is beneficial in the relief of symptoms of upper gastrointestinal discomfort. The comment stated that the acetylsalicylate has a therapeutic effect on the inflamed gastrointestinal tissue, and that if more data are needed the ingredient should be placed in Category III while the data are being collected. The data submitted were derived from experiments in labora-

tory animals. They included studies showing that aspirin lessened experimental peritonitis in the mouse and rat in addition to a study in cats. These studies indicate that aspirin may have an anti-inflammatory effect in the viscera. The comment stated that additional evidence conclusively establishing the precise role which acetylsalicylates play in the relief of upper gastrointestinal symptoms will require further development in methodology.

The Commissioner concludes that this data base, limited to studies in laboratory animals, is not adequate evidence to allow the use of an antacid claim for a salicylate or to justify continued marketing for this use pending further testing. There are also other data which indicate that salicylates may cause gastrointestinal bleeding. It may well be that the dosage and method of administration determine the effect a salicylate will have, but until well controlled studies can adequately resolve the issue the Commissioner concludes that a product containing a salicylate may not be labeled for antacid use alone.

74. There was comment that the antacid monograph in § 331.30(g)(3) (formerly § 130.305(g)(3)) failed to recognize professional labeling for antacid/antiflatulent combinations.

The comment is correct. A new provision has been added to § 331.31(b) stating that an antacid/antiflatulent combination may contain the professional labeling allowed for antacids and antiflatulents, i.e., peptic ulcer and postoperative gas pain.

75. There was comment that the inactive ingredient(s) should be listed on OTC drug labels.

The Commissioner reiterates the conclusion stated in paragraph 28 of the preamble to the tentative final order that the issue of listing inactive ingredients on OTC labels would be considered by the National Drug Advisory Committee. This matter is inappropriate as a subject matter for the individual OTC monographs. The Federal Food, Drug, and Cosmetic Act does not presently permit the Food and Drug Administration to require the labeling of all inactive ingredients.

ANTIFLATULENT

76. There was comment that it was inappropriate to create an antiflatulent monograph in the tentative final order and that a new call for data should have been published.

The Commissioner is of the opinion that it was proper to consider the status of the ingredient simethicone since the record before him fully addressed the issue and opportunity for comment and a public hearing on the matter were provided. Paragraph 67 of the preamble to the tentative final order stated that any other ingredient for consideration as an antiflatulent should be submitted to the Miscellaneous Internal Panel.

77. There was comment objecting to the limitation of antacid products containing simethicone to a use solely for concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion. The comment requested that the monograph allow an antacid claim alone, even though the product also contains the antiflatulent ingredient.* * *

Mr. FOUNTAIN. I might say I am raising this question so you can put your own explanation into the record.

Mr. HUTT. Surely.

Mr. FOUNTAIN. You ought to have that opportunity.

I think it had been reported in the press that you had at one time represented a client who manufactured an antacid/analgesic combination drug. Is that information correct?

Mr. HUTT. Yes, sir. In fact, I represented probably over the years a number of different clients who manufactured all types of foods, drugs, devices, and cosmetics.

Mr. FOUNTAIN. Did you represent Miles Laboratories?

Mr. HUTT. Yes, I did.

Mr. FOUNTAIN. When did you last represent them?

Mr. HUTT. I really have not the vaguest idea. It was some time before I came to the agency. I would have to ask the firm if you really

wanted detailed information. I had not thought of that kind of issue in over 4 years.

Mr. FOUNTAIN. How long have you been in Government service?

Mr. HUTT. Four years.

Mr. FOUNTAIN. Where did you come from?

Mr. HUTT. I came from private law practice, the law firm of Covington & Burling. There was, I might add, a full day's hearing on this matter before a Senate committee when I came to the Food and Drug Administration.

Mr. FOUNTAIN. Were all of these issues brought out?

Mr. HUTT. All of these issues were brought out at that time.

I would urge you, Mr. Chairman, to take a look at that hearing because—again I did not come prepared on this today—I laid out very clearly the fact that in spite of the lack of any requirement in Federal law that I disqualify myself from anything that I would disqualify myself from petitions, cases, and other similar matters on which anyone at Covington & Burling had worked while I was there involving the Food and Drug Administration.

I did that on the basis of the general canons of ethics and my feeling about what was a proper thing to do.

I might say that included such matters as the *Ornex* case, even though while I was at the law firm I had nothing to do with that case.

Mr. FOUNTAIN. I think you did the right thing. I did not mean my questions to imply directly or indirectly that in any of your actions here you have been influenced by that association. I am simply trying to get the record straight.

Mr. HUTT. Certainly.

Mr. DRINAN. If I may have a clarification. You disqualified yourself in the *Ornex* case because Covington & Burling had actually represented that particular manufacturer.

Had that law firm represented Miles Laboratories?

Mr. HUTT. The firm had, yes. I was there in the firm at that time.

Mr. DRINAN. What is the distinction? Why disqualify yourself in *Ornex?*

Mr. HUTT. That was a public proceeding, and the case was a formal matter where the firm had participated.

The fact of the matter is that any large law firm will advise or represent over a period of time any number of individuals on many different kinds of issues, indeed on occasion on different sides of the same issue.

Mr. DRINAN. Who represented Miles Laboratory all during the Alka-Seltzer controversy?

Mr. HUTT. I do not know. I cannot state for a certainty.

Mr. DRINAN. Covington & Burling?

Mr. HUTT. I have no particular knowledge that they ever entered an appearance at any time. If they did I shall put that in the record, Father Drinan.

I can state this: I do not recall ever talking to anyone from Covington & Burling who was at that time speaking to me about Alka-Seltzer on behalf of Miles Laboratories.

I think, as a general matter, that the firm still does work for Miles Laboratories, and may well, for all I know, indeed it is probable, that they did work on the Alka-Seltzer issue. However, I do not know

whether they appeared at advisory committee meetings with the firm representing them on that issue.

Mr. FOUNTAIN. I may have misunderstood you. I thought you said Miles Laboratories was at one time your personal client.

Mr. HUTT. I did personal work on some of their issues, yes, as well as, I might add, other companies who had antacid products pending before the panel.

Mr. FOUNTAIN. They were represented by your firm at the time you left the firm?

Mr. HUTT. To the best of my knowledge, yes.

Mr. FOUNTAIN. Why did you tell the subcommittee just a few moments ago you didn't have the vaguest idea?

Mr. HUTT. The question was whether Covington & Burling, as I understood the question, had represented, before FDA, Miles Laboratories on the Alka-Seltzer issue.

Whether the law firm was working for Miles Laboratories in relationship to those matters is to my knowledge not absolutely certain, although it is entirely probable.

I would suggest you ask Covington & Burling how they have or have not advised or represented them.

Mr. FOUNTAIN. I don't know how material it is. I am only trying to complete the record.

Mr. HUTT. Let me ask Mr. Yingling whether at the advisory committee meetings he recalls that Covington & Burling did represent Miles Laboratories. I simply do not know.

Mr. YINGLING. My recollection is that Miles Laboratories brought house counsel. If they were using any outside counsel they never spoke at any of the meetings and never appeared at the beginning. How they put their presentation together I don't know. I never met anyone from Covington & Burling during the proceedings or any other law firm to the best of my knowledge.

Mr. HUTT. Needless to say that does not mean that Covington & Burling was not advising Miles. They may well have been.

As I already said, they probably were.

Mr. FOUNTAIN. Was Alka-Seltzer one of the products you personally handled for Miles when you were with Covington & Burling?

Mr. HUTT. No, that was handled by other people in the firm.

Mr. FOUNTAIN. But you have worked in connection with Miles Laboratories in your capacity as General Counsel with the Food and Drug Administration.

Mr. HUTT. In connection with what?

Mr. FOUNTAIN. Miles Laboratories.

Mr. HUTT. I am sorry.

Mr. FOUNTAIN. As it relates to Alka-Seltzer.

Mr. HUTT. Only in this sense: I have not involved myself in any of the scientific issues. To the extent that this process affects all over-the-counter drug manufacturers, obviously it affects Miles and it affects other former clients.

I might add, as I have said many times, if I were in some way accused of having come to the Food and Drug Administration to protect the over-the-counter drug industry I guess I could best be accused of being extraordinarily unsuccessful. I certainly would not

have spent so much time and effort on the over-the-counter drug review which has succeeded in the area of antacids and antimicrobials to find a great many products unsafe, ineffective, or misbranded.

Mr. FOUNTAIN. I have a question for Dr. Schmidt which I shall have to withhold in view of his absence. However, he may already have answered this question in saying he assumes full responsibility for the decisions made.

The December 9 meeting was the panel's last formal meeting. Is that correct?

Mr. HUTT. Yes, there was a meeting by telephone.

Mr. FOUNTAIN. You can explain that as you go along.

Mr. HUTT. All right.

Mr. FOUNTAIN. FDA files contain summary minutes of a telephone conference with the panel on January 9, 1973, a copy of which I am placing into the record.

[The summary minutes referred to follow:]

FOOD AND DRUG ADMINISTRATION, BUREAU OF DRUGS

OTC PANEL ON ANTACIDS

(Telephone conference call January 9, 1973)

Chairman: F. J. Ingelfinger, M.D. (Massachusetts).
Members of the panel present:
H.C. Ansel, Ph. D. (Georgia).
M. I. Grossman, M.D. (California).
S. C. Harvey, Ph. D. (England).
E. W. Moore, M.D. (Colorado).
J. F. Morrissey, M.D. (Wisconsin).
Member of the panel not available: H. M. Spiro, M.D.
FDA participants: G. L. Yingling, Esq. (Maryland).
Part-time:
P. B. Hutt, Esq. (Maryland).
M. Novitch, M.D. (Maryland).
Acting Executive Secretary: A. M. Welch (Maryland).
Liaison representatives:
Consumer—A. Dickinson (Maryland).
Industry—J. Pisani, M.D. (Maryland).

These summary minutes are for the January 9, 1973, OTC Antacid Review Panel's telephone conference call. They were approved and adopted on March 1, 1973. Whenever there is a lack of unanimity on any point under discussion, the vote will be reported. Regulations do not permit voting by the Executive Secretary or any of the Liaison Representatives.

FRANZ J. INGELFINGER, M.D.,
Chairman.

Previous to this conference call, it had been determined that it was more appropriate for the labeling of magnesium products to contain the warning statement when the maximal daily dose exceeds 50 mEq.

This conference call was arranged to review and revise where appropriate, the December 22, 1972 draft of the Panel's Report.

Changes were made concerning the Antacid-Analgesic combination labeling on page 43. Clarification of how to determine the twenty-five per cent of any one ingredient was made on page 18. The kaolin statement on page 54 was amended to include by reference the comments made under aluminum regarding the untoward effects on absorption of other drugs. Other language changes were discussed and made. Review of the two draft documents clearly indicate the changes that were made.

The Panel Chairman will decide whether another meeting or conference call is necessary after the revisions of the December Draft are distributed to the Panel members.

Mr. FOUNTAIN. Mr. Hutt, you are shown to have participated on a part-time basis.

FDA informed the subcommittee that the telephone conference lasted 3 hours and included panel members in England, Colorado, Wisconsin, Los Angeles, and Boston. It that correct?

Mr. HUTT. Yes, indeed. We had particular trouble with the member in England because the satellite kept going around the face of the Earth and we lost contact with him.

Mr. FOUNTAIN. Page 2 of the summary minutes gives the reason for the conference call as follows: "This conference call was arranged to review and revise where appropriate, the December 22, 1972, draft of the panel's report." The remainder of the minutes for this 3-hour conference are 10 lines long and devote only one sentence to antacid/analgesic combinations, namely, and I quote: "Changes were made concerning the antacid-analgesic combination labeling on page 43." The minutes do not reflect the nature of the changes made, nor the nature of the discussion which resulted in those changes.

During the telephone conference concerning the antacid/analgesic combination portion of the panel's report, were any changes made on pages other than page 43?

Mr. HUTT. Perhaps Mr. Yingling can answer that.

Mr. FOUNTAIN. Mr. Yingling?

Mr. YINGLING. If my memory serves me correctly, the panel had made a change as far as page 43. They had also discussed page 22, and I believe page 46.

Then I think the minutes themselves show a clarification was made on pages 18 and 54. Therefore, there were a number of issues which the panel discussed, including a number of typographical changes made in the report itself for clarification.

Mr. FOUNTAIN. Were any changes made on the analgesic/antacid preparations only? Were there changes other than shown on page 43?

Mr. YINGLING. No, sir, not as I remember.

Mr. FOUNTAIN. Would you say this conference call was in the nature of a closed panel meeting? Would that be correct?

Mr. YINGLING. Yes, sir, this was done the same way.

Mr. FOUNTAIN. Of course, the Advisory Committee Act which went into effect on January 1, 1973, required detailed minutes of meetings, and we have made reference to this requirement a number of times.

I would like to ask this: Do you regard this one sentence on analgesic/antacid combinations to constitute detailed minutes with respect to what transpired in the conference call concerning these combinations?

Mr. HUTT. The way I recall this unfolding, it was a confirmation of a number of earlier telephone calls and written materials sent out. I would be the first one to admit that this might well justify a paragraph instead of a sentence, Mr. Chairman. I will not try to say this is a "detailed" discussion of the subject.

However, if you put it together with the earlier events I think it is more understandable. Those begin back on January 3.

Mr. FOUNTAIN. You said it was Telstar which to some extent interfered?

Mr. HUTT. Yes.

Mr. FOUNTAIN. How long were you unable to communicate? Were you cut off a good portion of the time?

Mr. HUTT. That was only from England.

Mr. FOUNTAIN. You still engaged in conversation with the others.

Mr. HUTT. Yes; and every time he blacked out and came back in, if I recall, and I was not there the entire time, he was filled in on what had happened.

Mr. FOUNTAIN. Judging from a memorandum in the FDA files, which I shall place in the record shortly, a draft of the panel's report was completed on December 22, 1972. I believe I asked this.

Mr. HUTT. In any event, that is correct.

Mr. FOUNTAIN. Did that draft reflect the panel's December 9, 1972, decisions with respect to antacid/analgesic products such as Alka-Seltzer?

Mr. HUTT. Yes, sir.

Mr. FOUNTAIN. Records in FDA's files disclose that the panel's December 22, 1972, draft report may have reached Miles Laboratories, the manufacturer of Alka-Seltzer, even before the panel itself had an opportunity to review it, since Miles had already reviewed it and prepared comments by December 29, 1972.

These records show that within approximately 2 weeks after the panel completed its draft report of December 22, 1972, a folder containing documents and memorandums relating to the report and its impact on Alka-Seltzer, was personally delivered to Mr. Gary L. Yingling, at that time director of OTC review.

Mr. Hutt, are you aware of the delivery of that folder to Mr. Yingling?

Mr. HUTT. I am now, yes.

Mr. FOUNTAIN. Were you at the time?

Mr. HUTT. At the time? I personally have no recollection of it. The difficulty again is trying to recall events 3 years after the fact.

I would suggest that if you like we might lay out what we believe are the events as they occurred.

If you would like us to go through that we would be happy to.

Mr. FOUNTAIN. If you would like to do it. However, to the extent we do not, you can feel free to fill in and complete the record.

Mr. HUTT. Very well.

The first comment I would make, then, is to the best of our knowledge that was not delivered to Mr. Yingling on December 29.

Mr. FOUNTAIN. The folder was identified only by a sticker label marked "Memorandum, December 29, 1972."

Handwritten on the sticker label are the words: "Given to me personally. GLY."

I am placing portions of the folder's contents into the record, consisting of:

(1) A three-page memorandum dated January 3, 1973, headed, and I quote: "Notes for presentation by the Commissioner to Dr. Ingelfinger."

(2) A December 29, 1972, memorandum entitled: "Comments on the Proposed Draft Report of FDA's Advisory Review Panel on OTC Antacid Drugs Dated December 22, 1972."

(3) A December 22, 1972 memorandum, on FDA stationery, to members of the OTC Antacid Review Panel and Industry Liaison on the subject of the Final Proposed Draft Report.

(4) A copy of the Panel's December 22, 1972, draft report, annotated to show Miles' objections to the panel statements affecting Alka-Seltzer, and suggested revisions to overcome these objections.

Presumably, the annotations were prepared by Miles Laboratories or one of its representatives.

Mr. HUTT. I presume so.

[The documents referred to follow:]

JANUARY 3, 1973.

NOTES FOR PRESENTATION BY THE COMMISSIONER TO DR. INGELFINGER

1. It is essential—from the viewpoint of the FDA, Miles and the success of the entire O-T-C Review program—that the deficiencies in the current Draft Report with respect to Alka-Seltzer be remedied promptly. We hope that Dr. Edwards can, preferably by a personal meeting, impress this point on Dr. Ingelfinger. Although Dr. Edwards has the right, and indeed the obligation, to remedy errors in the Panel's proposal, it really makes more sense to try to have the Panel correct the problems itself.

2. In talking to Dr. Ingelfinger, Dr. Edwards should emphasize that the Antacid Panel has done a fine job in the main, for which he is grateful, but that it is essential that the Report be one that is defensible not only as an expression of the Panel's scientific opinion but also legally and as a proper approach to self medication. Unless the Report can be so defended, it will put the whole O-T-C program in jeopardy. Because of this overwhelmingly important consideration, Dr. Edwards is talking to Dr. Ingelfinger.

3. The four areas which Miles believes must be corrected are summarized as follows. If feasible, Dr. Edwards should ask Dr. Ingelfinger to remedy all four problems. If practically this is impossible the order of priority is stated below. First, the unjustified implication that Alka-Seltzer is unsafe should be eliminated. This means modifying the material at pages 43 and 45–46 of the Draft Report.

The simple fact here is that Miles has submitted valid studies showing the safety of its product and 40 years of extraordinary safety in use, and the Panel has apparently disregarded these studies and relied on the Jennings letter and impressions relating to aspirin. Aside from the fact that this approach is legally indefensible, it is also scientifically wrong. Specifically, the reference to the Jennings letter should be deleted and the warnings and other aspersions presented in the Draft Report cannot be made applicable to Alka-Seltzer.

Second, sodium acetylsalicylate in a buffered solution should be included in the list of Category III ingredients (the only conceivable reason why this has not been done could be on the assumption that there is a safety problem for this ingredient; Miles' submissions show that this is not the fact). Miles should be given the same treatment for this ingredient as are its competitors.

Third, "upset stomach" should be added as a proper indication for antacids in Category I. The fact is that this is the term most commonly used by the consumer in describing his symptoms. The regulations themselves require the use of terms which could be read and understood by the ordinary individual.

Fourth, an exception should be made permitting a somewhat lesser amount of an additional ingredient than 25% of the total neutralizing capacity of the product where such an ingredient, nevertheless, makes an essential or valid contribution to the effectiveness of the product. The regulation merely requires that each active ingredient make a contribution to the claimed efficiency.

4. Dr. Compton is talking to Dr. Edwards as doctor to doctor and as Miles' Chief Executive to the Head of FDA. It is essential for each of them that these matters be corrected. Dr. Compton is not talking as a lawyer but should mention that from the viewpoint of his lawyers the bad treatment of Alka-Seltzer is legally indefensible. The main point is that it should be corrected as a matter of sense and policy.

5. In a marked up copy of the Draft Report, Miles indicated the drafting changes which should be made. Miles is, of course, not wedded to this particular drafting and Dr. Compton can have his lawyers meet with FDA people at any time to discuss the niceties of drafting. The important point, however, is that Dr. Edwards convince Dr. Ingelfinger of the desirability of making the changes in the Panel's Draft Report before it is submitted finally to the Commissioner.

MEMORANDUM—DECEMBER 29, 1972.

COMMENTS ON THE PROPOSED DRAFT REPORT OF FDA'S ADVISORY REVIEW PANEL ON OTC ANTACID DRUGS DATED DECEMBER 22, 1972

Our concern with the proposed Draft Report of FDA's Advisory Review Panel on OTC antacid drugs dated December 22, 1972, may be expressed in the following three points:

(1) The first point relates to the safety of Alka-Seltzer for use in home medication. Specifically, the Draft Report requires the insertion of a warning statement which is wholly inappropriate to the public's use of Alka-Seltzer and which would only serve to confuse the consumer. Further, inaccurate and inappropriate derogation of the safety of Alka-Seltzer is found in ascribing to its use harm which is alleged to result from aspirin in combination with an antacid. This fails to take cognizance of the fact that, as Alka-Seltzer is taken, and the only way it can be taken by the public, aspirin is not present. Instead, a reaction mixture of a buffered solution of sodium acetylsalicylate together with dissolved antacid is taken, and this reaction mixture in its action in the stomach is wholly to be differentiated from aspirin in its solid form. This issue has been detailed in marginal note comments in Appendix A at pages 9, 43, 45–46, and 70.

(2) To the degree that the combination of upset stomach indications with analgesic indications is recognized, provided that safety in use is not brought into question by the warning statement referred to above, the effectiveness of Alka-Seltzer in use for home medication would appear to have been accepted by the Panel. We are concerned, however, that in fact Alka-Seltzer is widely used by the public for upper gastrointestinal symptomatology without other concurrent symptoms, and we are convinced this rests on valid grounds relative to the whole formulation. We are prepared to recognize that the submission of further evidence in this area may be desirable and we would accept, if it were deemed essential under the format of the OTC regulations as issued, Category III application to this issue. This issue has been detailed in marginal note comments in Appendix A at pages 40, 50, 56, 57, and 67.

(3) In a probable effort to minimize the use of a multitude of antacid ingredients, a technical requirement that each ingredient contribute at least 25% of the total neutralizing capacity of the product has been added in the Draft Report. We feel that an exception to this should be allowed where an essential or valid contribution may be made relative to a somewhat lesser amount of an additional ingredient. This issue has been detailed in marginal note comments in Appendix A at pages 18 and 61.

For convenience, a marked-up copy of the proposed Draft Report of FDA's Advisory Review Panel on OTC antacid drugs dated December 22, 1972, has been attached as Appendix A with those paragraphs which relate to the above three areas of concern underlined in red and with marginal notes. These may be found on pages 9, 18, 40, 43, 45–46, 50, 56, 57, 61, 67, and 70.

Within the meaning of the above three issues the following detailed explanatory comments explain the problem more fully.

The monograph as presently written would severely limit the indications for Alka-Seltzer and sharply curtail its usefulness in home medication. To correct this improperly adverse effect on Alka-Seltzer, the proposed Draft Report should be modified in the following regard:

(1) Recognition should be given to the fact that home medications are for laymen and must be capable of use without the intervention of a professional. In this sense, cognizance should be taken of the terminology which the layman most commonly uses in attempting to express his upper gastrointestinal tract discomfort, and for which he seeks assistance with his household remedies. Accordingly, "upset stomach" should be added as a proper description of the symptoms for which this class of products is indicated. The Panel has eliminated the term "upset stomach" as a description of the symptoms for which an antacid is used for home medication, accepting only "acid indigestion," "heartburn," and "sour stomach." Our experience and consumer surveys show that the term most frequently used by the consumer is "upset stomach." This data was included in our submissions.

(In her oral testimony before the Panel Dr. Dorothy Carter summarized evidence which shows that in order to accommodate consumer usage, upset stomach should be recognized as a valid antacid indication. She stated as follows:

"The term upset stomach is not a precise medical term but is a term used by the layman to describe upper gastrointestinal discomforts. A recent study of

consumer attitudes by Motivational Programmers showed that when consumers describe problems and actual feelings for which they used a variety of antacid products including Alka-Seltzer, the most frequent response by the consumer to the description of the problem for which he took the product was upset stomach, followed by indigestion and heartburn. A further study by this group just concluded a few days ago demonstrates that upset stomach is the most frequently mentioned symptom term for which major OTC brands of antacids are used. While occasionally terms such as acid indigestion and heartburn were used, sour stomach is seldom used.")

(2) The manner in which the Draft Report authorized the labeling of Alka-Seltzer for concurrent symptoms is unrealistic for home medication labeling and requires modification. Under the Draft Report, we would have to say something like this: "For relief of acid indigestion (or heartburn or sour stomach) and headache (or other analgesic claim); do not use this product for the treatment of acid indigestion (or other antacid claim) unless this symptom is accompanied by headache (or other analgesic claim.)"

This kind of labeling could only serve to confuse the consumer and would vitually limit Alka-Seltzer to the analgesic field, despite the fact that Alka-Seltzer has a clear and proper place for the relief of "upset stomach" and other antacid symptoms. Our submissions show that Alka-Seltzer is safe and effective for the concurrent symptoms and there is no justification for confusing the consumer by having these indications negatively restated as a warning.

(3) In our submissions of data to the Panel, and specifically as summarized in the testimony of Dr. Dorothy Carter, which is attached as Appendix B, we have demonstrated that there is an appropriate effectiveness of Alka-Seltzer as a home remedy in mild upper gastrointestinal discomfort and we are convinced that this relates to more than its clearly demonstrable antacid effect. The public so uses it and there is good supportive evidence to indicate that this usage is proper. Consequently, there is good basis for recognizing this usage in Category I. Technically perhaps, under the regulatory program under which the Panel deliberations are conducted, this usage which relates specifically to sodium acetylsalicylate could be treated in Category III, but at a minimum should be explicitly recognized there. Without its recognition, the interim use of the whole preparation for relief of upper gastrointestinal discomfort might seem to be prohibited; this derives from statements relating to aspirin in Category II and relating to analgesics in Category I. This comment is over and above the quite proper role of Alka-Seltzer as a combination drug for conjoint symptom usage.

Underlying the restrictions which the Draft Report would impose on Alka-Seltzer, and most prejudicial, is the implication that Alka-Seltzer is unsafe because of the aspirin content of the dry tablet, unless its use be restricted. This implication is not based on proper scientific evidence and in fact is contradicted by the controlled and statistically valid scientific evidence we have presented in our written and oral submissions. These materials show in great detail that dissolved sodium acetylsalicylate in the buffered antacid solution of Alka-Seltzer is in fact wholly different, both chemically and in its physiological behavior, from the water-insoluble acidic form of aspirin; perhaps most noteworthy is simply and explicitly that it does not cause gastric bleeding. Clearly from this, we most strongly object to paragraph II (c) (1) on pages 45–46 in its wholly improper application to Alka-Seltzer, though as it relates to aspirin in its acid form intended to be taken as such in solid form, it may have merit.

Unfortunately, the Panel did not have available to it a paper which will shortly be published in the American Journal of Digestive Diseases by Dr. Allan R. Cooke, Associate Professor of Internal Medicine in the Division of Gastroenterology at the University of Iowa. This paper has direct bearing on and is supportive of our position on the issues cited. Accordingly, a preprint is attached as Appendix C. In this paper, entitled, "The Role of Acid in the Pathogenesis of Aspirin-Induced Gastrointestinal Erosions and Hemorrhage," Dr. Cooke made an extensive review of the literature of aspirin and its effect on the stomach. He concluded that the basis of aspirin damage to the gastric mucosa (exfoliation, erosions, occult and overt bleeding) is the presence of acid in the lumen of the stomach. When aspirin is in an unbuffered water-insoluble acidic form it increases gastric mucosal permeability which results in cell damage, exfoliation and erosions. The nature and severity of the gastric erosions and progression of occult bleeding to overt bleeding induced by the acid form of aspirin depends upon a variety of factors some of which are dose, dose form, ethanol, ascorbic acid levels and bleeding disorders. However, when the aspirin is present as the water-soluble acetylsalicylate salt, buffered so that gastric acidity is neutralized, it does not change mucosal permeability or cause damage to the stomach.

The Draft Report seems to disregard the material in our submissions. The Panel does cite and relies upon a 1963 communication to the editor by Dr. Jennings found in the British Medical Journal which reports his review of his cases of gastrointestinal bleeding indicating the number which he thought were due to aspirin-containing preparations, including Alka-Seltzer. It is noteworthy that no supportive data accompanied this communication. The Jennings letter appears to be no more than clinical impression based solely on the erroneous assumption that a solution of Alka-Seltzer operates in the stomach in the same way as ordinary aspirin. It was written before we had published data which clearly shows a fundamental distinction between buffered sodium acetylsalicylate as contained in a solution of Alka-Seltzer and the acid form of aspirin.

The association between Alka-Seltzer and overt bleeding which is referred to in the Jennings letter derives from the association between aspirin and overt bleeding which has been drawn most strongly in England, and therefore it is natural that the association of Alka-Seltzer with overt bleeding would occur in the British literature and in reports made in England directly to the Company. Our investigation of these reports has almost always established that Alka-Seltzer was implicated merely because of the aspirin content of the dry tablet of Alka-Seltzer and the association in the literature between aspirin and overt bleeding; data suggesting a causal relationship is invariably absent. In a condition as complex as overt bleeding where the etiological factors are so widespread, clinical impressions based merely on the aspirin content of the dry tablet of Alka-Seltzer cannot be considered as credible scientific evidence.

The Jennings letter or any similar suggestions about Alka-Seltzer as a cause of overt bleeding in the stomach cannot be accepted in contradiction of the extensive controlled studies supporting the safety of Alka-Seltzer.

In his paper, which is attached at Appendix C, Dr. Cooke critically reviewed the epidemiological data associating aspirin with overt bleeding and found the data to be controversial. However, it has been found consistently that the acute lesion group have a high proportion of people who took aspirin shortly before admission to hospital with bleeding. Since our data demonstrated that Alka-Seltzer does not produce gastric lesions, Alka-Seltzer would not be liable to cause overt bleeding.

There is no scientific basis for assuming that Alka-Seltzer can cause overt bleeding in the absence of special circumstances such as pre-existing blood disorders. In his testimony before the Panel Dr. Cooke summarized data from controlled and statistically valid studies which convinced him that "the mixture of sodium citrate and sodium acetylsalicylate contained in the Alka-Seltzer solution is safe."

The complete oral testimony of Dr. Cooke is contained in Appendix D.

The basic distinction between sodium acetylsalicylate in Alka-Seltzer and aspirin was discussed by Dr. Cooke with a member of the Panel in the course of his testimony. Dr. Morrissey pointed out to Dr. Cooke that all physicians such as himself who see cases of hematemesis in hospitals find numerous instances of aspirin ingestion beforehand, i.e., associated with such gastrointestinal bleeding. He then stated that he believed there were some such cases involving Alka-Seltzer. Dr. Cooke responded by indicating that his review of the literature indicated that the relationship between aspirin and gastrointestinal bleeding is controversial.

At best the evidence suggests there is a relationship between gastric erosions and aspirin, and the association between aspirin and gastrointestinal bleeding is strongest in the acute erosion group. Since it had been shown that Alka-Seltzer did not cause gastric erosions, there is no basis for assuming that Alka-Seltzer causes gastrointestinal bleeding. He then went on to point out that such instances of unproved association between Alka-Seltzer ingestion and hematemesis were in his judgment a result of the fact that physicians have not understood the differences between the reaction mixture of a solution of Alka-Seltzer and aspirin products. The generally existing bias against aspirin in these situations caused confusion in the physician's mind, which coupled with ignorance of the differences between Alka-Seltzer and aspirin, resulted in the suggestion that Alka-Seltzer had in some way been related to hematemesis. He further stated that this association is contraindicated by the evidence, which indicates quite strongly that Alka-Seltzer, unlike aspirin, does not cause mucosal damage or gastric bleeding.

Finally, it is hard to square the implication of Alka-Seltzer as a potential hazard in the light of its record of safety. In our testimony to the Panel we pointed out that over a period or more than 40 years we have produced and sold more than

70 billion tablets. Our experience over the last seven years, for which we have an accurate list of complaint letters, and during which time we have sold over 600 million packages of Alka-Seltzer in the United States alone, demonstrates that the product has a phenomenal safety record. Only 89 instances of possible adverse reaction were reported in the United States during this period. This is an average of only 15 safety-related complaints per 100 million packages. We think it is fair to say that this record is inconsistent with any assertion that Alka-Seltzer, in any of its current usages, is a hazard to the public.

ADRIEN L. RINGUETTE.

MEMORANDUM

APPENDIX A

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
December 22, 1972.

To: Members of OTC Antacid Review Panel and Industry Liaison.
From: Director, OTC staff (BD–109).
Subject: Final proposed draft report.

Enclosed you will find the final proposed draft report of the Advisory Review Panel on over-the-counter antacid drugs.

You will note the removal of the aluminum warning statement and other additional minor changes.

The OTC Staff needs to verify the citation appearing on Page 17 by O. Kornborg.

We will be calling you within the week to arrange a telephone conference call for the first or second week in January.

GARY L. YINGLING, Esq.

Enclosure.

cc: F. Ingelfinger, M.D.
H. Ansel, Ph.D.
M. Grossman, M.D.
S. Harvey, Ph.D.
E. Moore, M.D.
J. Morrissey, M.D.
H. Spiro, M.D.
J. Kirsner, M.D.
A. Relman, M.D.

Reprinted by the Proprietary Association.

(Draft Dec. 22, 1972)

REPORT OF THE ADVISORY REVIEW PANEL ON OVER-THE-COUNTER ANTACID DRUGS TO THE COMMISSIONER OF FOOD AND DRUGS, JANUARY 1973

Reprinted by the Proprietary Association.

INTRODUCTION

In the Federal Register for January 5, 1972 (37 F.R. 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness, and labeling of all over-the-counter (OTC) drugs by independent advisory review panels. The same day the Commissioner published a request for data and information on all active ingredients utilized in antacid products (37 F.R. 102).

On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review (37 F.R. 9464), which were made effective immediately. An additional 30 days were allowed in the preamble to those final regulations for interested parties to submit data on antacid drugs.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC antacid products pursuant to the requirements of the regulations:

Franz J. Ingelfinger, M.D., Chairman
Howard C. Ansel, Ph. D.
Morton I. Grossman, M.D.

Stewart C. Harvey, Ph. D.
Edward W. Moore, M.D.
John F. Morrissey, M.D.
Howard M. Spiro, M.D.

The Panel was first convened on February 22, 1972, in an organizational meeting. Five working meetings were held, on May 8, June 21, 22, and * * *

* * * * * * *

The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor *otherwise useful for its non-antacid action in the relief of upper gastrointestinal symptoms or in its adjuvant or corrective properties* will contribute to the product's safety and effectiveness for use in antacid therapy alone. The addition of non-antacid or non-corrective ingredients may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor *otherwise useful for its non-antacid action in the relief of upper gastrointestinal symptoms or in its adjuvant or corrective properties* should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and non-antacid ingredient. This dual indication should be clearly stated on the product label.

* * * * * * *

[Pages 43, 43 Revised, 44, 45, 46.]

(Page 43)

NOTE.—The first two paragraphs in Section 1.D. have been rewritten in order more clearly to illustrate the insertions which are suggested to be made therein and which are underlined in blue ink.[1] These insertions replace the phrase "a corrective for an antacid side effect" and are necessary in order for these paragraphs to conform to the language contained in page 50.

D. *Drugs combining antacid and other active ingredients*

The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor *a corrective for an antacid side effect*, will contribute to the product's safety and effectiveness for use in antacid therapy alone. The addition of non-antacid or non-corrective ingredients may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor *a corrective for an antacid side effect* should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and non-antacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief of both of the active ingredients. The dual indication should clearly be stated on the label [and the label should include a prominently displayed warning that such a combination shall not be used for the treatment of heartburn and/or indigestion and/or sour stomach unless these symptoms are accompanied by indications for an analgesic.].[2] Such a product is not appropriate for peptic ulcer and related * * *

NOTE.—The use of Alka-Seltzer for upset stomach and symptoms which indicate the use of an analgesic is safe and effective. No such warning is appropriate.[3]

(Page 43, Revised: 1/3/73)

D. *Drugs combining antacid and other active ingredients*

The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor a cor-

[1] Blue ink underlined portions in the original appear in italic.
[2] Bracketed material indicates portions crossed out in Miles Laboratories' submission.
[3] In the original submission, Miles Laboratories' "Note" appear in the left hand margin next to the pertinent portions of the draft report.

rective for an antacid side effect, will contribute to the product's safety and effectiveness for use in antacid therapy alone. The addition of non-antacid or non-corrective ingredients may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor a corrective for an antacid side effect should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and non-antacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief provided by both types of active ingredients. The indication section of the labeling should state clearly that the combination should be used only when heartburn and/or acid indigestion and/or sour stomach are accompanied by indications for an analgesic. Such a product is not appropriate for peptic ulcer and related * * *

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disorders. Any analgesic ingredient that is generally recognized as safe and effective (see analgesic Monograph) may be used as the analgesic ingredient.

2. The Panel concludes that it is rational to include a non-antacid laxative ingredient in an antacid if the laxative is solely for the purpose of counteracting the constipating action of one or more of the antacid ingredients. Any laxative action ingredient that is generally recognized as safe and effective (see laxative Monograph) may be used as the laxative ingredient. No labeling claim for the laxative effect would be truthful, because the amount of non-antacid laxative ingredient present should not cause laxation, but only counteract the constipating effect of the antacid.

Comment: Any other combination of antacid with non-antacid active ingredients should be permitted by the Food and Drug Administration only after it is shown that the conditions for a combination drug set out in the regulations have been met. The Panel is unaware of any other such combinations which meet these conditions at the present time.

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II. *Conditions Under Which Antacid Products Are Not Generally Recognized as Safe and Effective or Are Misbranded.*

The use of antacids under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Panel concludes that the ingredients, labeling, and combination drugs involved should be removed from the market until scientific testing supports their use.

A. *Active ingredients*

No active ingredients for which [Editor's note.—Handwritten notation not legible] not included in Category I or Category III has, in the Panel's opinion, been shown by adequate and reliable scientific evidence to be safe and effective.

B. *Labeling*

The Panel concludes that it is not truthful and accurate to make claims or to use indications on the package label that the product may directly affect "nervous or emotional disturbances", "excessive smoking", "food intolerance", consumption of "alcoholic beverages", "acidosis", "nervous tension headaches", "cold symptoms", and "morning sickness of pregnancy" since the relationship of such phenomena to gastric acidity is both unproven and unlikely.

C. *Drugs combining antacid and other active ingredients*

1. Although the panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for concurrent symptoms, it concludes that fixed

NOTE.—The *italicized* portion of Section II. C. 1 exhibits confusion between the reaction mixture of Alka-Seltzer and the dry ingredients from which the tablet is made. This paragraph should not apply to Alka-Seltzer. It fails to differentiate aspirin from a buffered solution of sodium acetylsalicylate. The underlined portion is only appropriate to the degree that it relates to a solid mixture of an antacid and aspirin in its acid form intended to be taken as such. It does not appropriately apply at all (for reasons already stated and supported by data submitted to the Panel) in referring to a reaction mixture containing the water soluble wholly dissolved sodium acetylsalicylate in a buffered solution.

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antacid-aspirin combinations are irrational for antacid use alone and therefore should not be labeled or marketed for such use. Not only are OTC antacids sometimes indiscriminately used, which may lead to aspirin toxicity with such combinations, but aspirin also has a potential for damaging the gastrointestinal mucosa by the topical action of breaking the mucosal barrier or by other mechanisms.

Citations: 1) Brodie, DA and Chase, BJ; "Role of Gastric Acid In Aspirin-Induced Gastric Irritation In The Rat", Gastroenterology, *53*:604–610, 1967.

2) Grossman, MI; Matsumoto, KK; Lichter, RJ; "Fecal Blood Loss Produced By Oral and Intravenous Administration of Various Salicylates", Gastroenterology, *40*:383–388, 1961.

3) *Jennings, GH: "Alka Seltzer and Haematemesis", Letter to the Editor; Brit. Med. J., 16:475, 1963*

NOTE.—Delete Jennings citation. See memorandum comment.[1] [2]

2. The Panel concludes that it is not safe and effective concurrent therapy to add an anticholinergic ingredient to an OTC antacid product, because optimal use of antacids and * * *

* * * * * *

[Pages 56, 57.]

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The Panel concludes that this ingredient is safe in the amounts usually taken orally, and believes it unnecessary to impose a specific dosage limitation at this time.

NOTE.—Add new paragraph 11 setting forth rationale for usefulness of sodium acetylsalicylate and affirming its safety.

B. *Labeling*

1. OTC products containing ingredients listed in Category I or III are often used to treat symptoms that are not known to be related to acidity of gastric contents. These products may or may not qualify as antacids by the *in vitro* acid neutralizing test. The symptoms include "indigestion", "gas", "upper abdominal pressure", "full feeling", "nausea", "excessive eructations", *"upset stomach"*, and the like. Some of these symptoms are vague, most are poorly understood as to pathophysiological mechanism, and none have been shown by adequate and reliable scientific evidence to be caused by or alleviated by changes in gastric acidity. The Panel concludes that companies marketing products that make claims for alleviation of these or other similar symptoms should within two years provide evidence of effectiveness, consisting of statistically valid clinical trials, in relieving each of these symptoms for which a claim is made. But no claim for

NOTE.—See note on page 40. "Upset stomach" should be regarded as an indication for the use of an antacid in Category I and should be deleted from this category.[1]

(Page 57)

acid neutralizing properties can be made unless the product meets the *in vitro* standard (see Monograph). Claims for those symptoms for which such evidence has not been provided by that time should be withdrawn.

Comments: This section pertains to the relief of upper gastro-intestinal symptoms claimed for an "antacid" product on the basis of action unrelated to its acid neutralizing capacity. For example, in a patient with total gastric anacidity, an agent might conceivably relieve gastric discomfort by altering gastroduodenal motor function.

2. The Panel concludes that claims or indications which link certain signs and symptoms, such as "sour breath", "upper abdominal pressure", "full feeling", "nausea", "stomach distress", "gas", "indigestion", *"upset stomach"*, and "excessive eructations" with normal or hypernormal gastric acidity, are unproven since the relationship of such signs and symptoms to gastric acidity is unknown or dubious and there is no adequate and reliable scientific evidence to support these claims. Such claims or indications encourage the user to draw conclusions as to the cause or intermedication of such symptoms, a conclusion that even the medical profession is incapable of drawing at this time. Therefore, those claims and indications that link these symptoms to acidity or "hyperacidity" should not be

[1] In the original submission, Miles Laboratories' "Notes" appear in the left hand margins next to the pertinent portions of the draft report.

[2] At this "note" there is a handwritten arrow with the word "out" pointed to the Jennings citation (3).

permitted unless supported by statistically valid clinical trials obtained within 2 years.

NOTE.—See note on page 40, "Upset stomach" should be regarded as an indication for the use of an antacid in Category 1 and should be deleted from this category.[1]

* * * * * * *

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RECOMMENDED MONOGRAPH

130.305 *Antacids*

An over-the-counter antacid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in section 130.302.

(a) *Active Ingredient(s).* The active ingredient(s) of the product consist of one or more of the ingredients permitted in paragraphs (2)—(14) within any maximum daily dosage limit established, each ingredient is included at a level that contributes *at least 25 percent* of the total acid neutralizing capacity of the product, and the finished product has a pH of 3.5 or greater at the end of the initial 10 minute period as measured by the method established in paragraph (1).

NOTE.—See note on page 18. Exceptions should be recognized as appropriate.[1]

* * * * * * *

[Pages 69 and 70.]

(Page 69)

(e) *Statement of active ingredients.*

(1) The labeling of the product contains the quantitative amount of each active ingredient, expressed in terms of the dosage unit stated in the directions for use (e.g., tablet, teaspoonful).

(2) The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq. (5mg.) or higher.

(f) *Neutralizing capacity.*

The labeling of the product provided to physicians (but not to the general public) contains the neutralizing capacity of the product, as calculated in clause (a)(1)(ii)(k), expressed in terms of the dosage recommended per minimum time interval or, if the labeling recommends more than one dosage, in terms of the minimum dosage recommended per minimum time interval.

(g) *Combination with non-antacid active ingredients.*

(1) An antacid may contain any generally recognized safe and effective non-antacid laxative ingredient (see laxative Monograph) to correct for constipation caused by the antacid. No labeling mention of the laxative ingredient or claim of laxative effect may be used for such a product.

(2) An antacid may contain any generally recognized safe and effective analgesic ingredient(s) (see analgesic Monograph) if it is indicated for use solely for the concurrent

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symptoms involved (e.g., headache and acid indigestion). *The label shall state: "Do not use this product for the treatment of (heartburn, acid indigestion, sour stomach) unless these symptoms are accompanied by (indications for an analgesic).*

NOTE.—This statement should be deleted. See note on page 40.[1]

(h) *Inactive ingredients.*

The amount of lactose in a maximum daily dosage may not exceed 5 gm. per day.

Mr. FOUNTAIN. Can you tell us when, and any of the circumstances under which the folder containing the memorandums and the documents were delivered to Mr. Yingling? Can Mr. Yingling give us that answer?

[1] In the original submission, Miles Laboratories' "Notes" appear in the left hand margins next to the pertinent portions of the draft report.

Mr. HUTT. Perhaps we can ask Mr. Yingling to go back to December 22, as was suggested a moment ago, and trace the steps as they went forward.

I would simply begin by saying that the dissemination of the December 22 draft was as I described it earlier, namely, it was given to the industry liaison and to the consumer liaison and each of them was asked to distribute it to anyone they wished to and to bring any comments back to the panel so that those comments could be discussed in the telephone conversation that subsequently took place.

Mr. Yingling can go through the chronology.

[The chronology referred to may be found in the appendix at pp. 363–364.]

Mr. FOUNTAIN. Mr. Yingling?

Mr. YINGLING. As you indicated, on December 22, 1972, the OTC staff mailed the final proposed draft report of the Advisory Review Panel on the Antacid Drugs to the panel members and liaisons.

Checking back into the occurrences, Dr. Mark Novitch's calendar shows a meeting was held with Mr. Adrien Ringuette and Mr. Charles Jolly of Miles Laboratory on January 5, 1973.

The calendar indicated Mr. Hutt was in attendance. There is no reference as to whether I was in attendance. I believe I was.

Mr. HUTT. My records do not show I was in attendance. I have no recollection of it.

Quite frequently on these meetings I would be asked to attend and Mr. Yingling would attend instead, but it is possible either that both of us were there or not.

Mr. FOUNTAIN. Your record shows Mr. Hutt was there?

Dr. NOVITCH. I am Mark Novitch. My records——

Mr. FOUNTAIN. Reading from your statement?

Dr. NOVITCH. Yes, sir.

Mr. YINGLING. It is my recollection I was at the January 5 meeting and I received at that time the volume in question from Miles Laboratory entitled "Memorandum, December 29, 1972" and I at that meeting, or shortly thereafter, wrote the note at the front of it saying it was given to me personally with my initials. That is the best of my recollection, sir.

Mr. FOUNTAIN. Did FDA make any use of the material in the folder?

Mr. YINGLING. No, sir. As I remember I took the volume back to my office, looked at it but did not have any other occasion to use it, forward it to anyone else, review it, comment on it, or do anything else.

Mr. FOUNTAIN. Did any FDA personnel, including members of the General Counsel's Office, discuss the receipt or contents of the folder with representatives of Miles Laboratories, or with the FDA Commissioner, or with any of the panel members?

Mr. YINGLING. It is my recollection when we received the document itself there was a discussion of what the document contained as far as the gentlemen from Miles going through and explaining what it was and the questions they were raising. That was the only discussion I remember having about the document at that time.

There was no subsequent discussion with anyone else.

Mr. FOUNTAIN. That is the full extent of the details?

Mr. YINGLING. That is my recollection.

Mr. HUTT. As far as the General Counsel's Office is concerned, the only person who might conceivably have looked at it or discussed it would have been myself. Again I do not recall either the document or being at the meeting.

Mr. FOUNTAIN. Were the contents of the folder made part of the administrative record of the antacid panel review and the subsequent regulations?

Mr. HUTT. No, sir. They would not have been because they were not submitted to the panel.

For that reason they were not included in the administrative record.

Mr. FOUNTAIN. You would not include it in the administrative record?

Mr. YINGLING. That was my decision. I was director of the OTC review. I had only the one volume. Submissions made to the panel were to be made in eight volumes. I thought it was an administrative document given to me to understand what the issues were as far as the review was concerned.

I did not feel it constituted part of the administrative records for the hearing clerk.

[See appendix, pp. 258–261 for submission by Plough, Inc., dated December 29, 1972, addressed to Mr. Yingling and hand delivered January 3, 1973, on the same subject as the Miles Laboratories submission—the antacid panel's December 22, 1972, proposed report and monograph. Plough's submission was made part of the administrative record.]

Mr. HUTT. If so, we would have been required to reproduce it, send it to the entire committee, and to put it in the hearing clerk's office and make it part of the official administrative record, and take into account everything that was in it.

I think from the nature of the document that would not have been the way to handle it. It simply did not add anything to the issues involved.

Mr. FOUNTAIN. You do not think it should have been made part of the administrative record?

Mr. HUTT. I honestly do not. It was not requested to be sent to the entire panel by the company as far as I can tell from looking at the document.

Moreover, inasmuch as it was received on the fifth I am not sure there would have been time to have done that.

Mr. YINGLING. The panel meeting was the ninth.

Mr. HUTT. We could not have gotten it out to the panel. If we decided to make it part of the administrative record we would have had to put off the telephone call in order to get it out to everybody and let them read it.

Mr. DRINAN. May I just clarify something here as to what date this took place between one or both of you and the general counsel of Miles?

Mr. YINGLING. January 5.

Mr. DRINAN. Did Miles Laboratories set this up?

Mr. HUTT. Yes.

Mr. YINGLING. Yes, sir. At the time the OTC drug review started there were a number of questions about how the review was being conducted. The OTC review, myself as director, had an open door

policy for anyone—consumers, industry, anyone who wanted to come in and discuss the review and how it was being done.

Therefore, anyone could call and request a meeting and we would gladly meet with them and just discuss the review overall, whatever problem they had, and any document they wished to bring in, and give it to us, we accepted.

Mr. DRINAN. Do you keep a record of all the lobbyists who come and what they say?

Mr. YINGLING. Not at the time. In the beginning, not a very good record was kept. I understand now the staff has a good record of who appears.

I must apologize, our record was not very good in 1972.

Mr. DRINAN. Did the members of the advisory committee know that the general counsel of Miles Laboratories had come in and lobbied you people?

Mr. YINGLING. Since the panel had already seen a Miles' presentation earlier at a panel session we did not discuss it with various panel members.

Mr. DRINAN. The five M.D.'s and two Ph. D.'s had no idea Miles Laboratories was trying to come in the back door to influence some decision. You never told them you had sat down and talked with them and you had received a document which you never gave the advisory committee?

Mr. HUTT. Father Drinan, again we ought to put this in context.

First, anybody in our opinion is entitled to come in and talk to the Food and Drug Administration about issues which concern them.

What we do about those issues is obviously another matter.

Second, this document, and I simply do not recall having seen it, but if I had received it, taking a look at it, it does not seem to me this was something that should become part of the administrative record, and particularly at that late date, 4 days before the final telephone call.

Certainly I do not see how it could have influenced the OTC review one way or another.

Now having read it I do not see how it could have influenced anybody, at least having read the cover memorandum and a couple pages.

Mr. DRINAN. When did this come to your attention?

Mr. HUTT. Just a few days ago, maybe 2 weeks ago.

Mr. DRINAN. Who kept it secret from the General Counsel of the agency?

Mr. HUTT. I do not think it is a question of being kept secret. We receive pieces of paper in the agency at an alarming rate and only important things would be brought to my attention.

Mr. DRINAN. Did the consumer agencies come to you during this critical period? Is there any record of that?

Mr. HUTT. Yes. On this particular one?

Mr. DRINAN. Yes.

Mr. HUTT. I know they used to call me and talk with me about the OTC review in general. Whether they came on this particular one I could not say.

Mr. YINGLING. The consumer representative, as I remember correctly, was out of town around the date the proposed monograph was sent out, so she had come to the FDA offices a couple days before

the telephone conference call and gone over the draft report and gone over the various issues involved and had been briefed.

Mr. DRINAN. I am not speaking of somebody who was on the panel because the general counsel of Miles Laboratory was not on the panel.

I am thinking of the broader consumer agencies. Did they come in and lobby?

Mr. HUTT. One of the problems we had, Father Drinan, was that even though we had an opportunity for anyone to appear before the panel and to come in and discuss it with us at any other time, many people did not take advantage of that.

The health research group, for example, which did object to the conclusions of the panel, never came in to the panel to give their views.

Mr. DRINAN. They are trying to get the documents in the court.

Mr. HUTT. They could have come in and presented their scientific evidence before the panel and attempted to convince the panel that their views were correct.

They did not use that opportunity. We invited everyone to come in. There was no single person in the United States or abroad who asked for an opportunity to appear before the panel and was turned down, no person at all.

Mr. DRINAN. But Miles Laboratory had a special interest in this because it is their product.

Mr. HUTT. That is correct.

Mr. DRINAN. Millions of dollars were involved. This document was received and they were able to lobby behind the backs of the advisory committee, so to speak. It just seems a little strange to me that——

Mr. HUTT. Father Drinan, again I would like to go back and talk about the timing here because this was received on January 5. It represents, if I may be a bit unkind, a naive approach at best. In fact, it is somewhat humorous at that late date to suggest that the entire panel and FDA change their approach on this matter.

Prior to receiving this, on January 2 or some time before January 3, the panel administrator, Mr. Armond Welch, had come in to see Dr. Novitch and had also talked to Mr. Yingling because he was concerned about the approach that the panel was taking.

He was an oldtime FDA employee, and is still with the agency, and he was very concerned about what he regarded as negative labeling, which the agency for many years had strongly opposed as being not sufficiently clear to consumers.

[An FDA memorandum on this subject may be found in the appendix at pp. 350–352.]

Mr. HUTT. On January 3 he called Dr. Ingelfinger and discussed with Dr. Ingelfinger whether new language might be acceptable that would eliminate the negative warning aspect of it and, instead, replace that with what he referred to as a limited indication, that is, the concurrent symptom approach.

Dr. Ingelfinger said that he thought that made more sense than the negative labeling approach and, as a result, Mr. Welch, on January 3, telephoned all of the other members of the advisory committee to raise the same issue with them.

Again, this has to be a function of the staff—not to say "FDA wants you to do this" but rather to say "Here is another issue which has arisen. Is this acceptable in lieu of the other way of doing it?"

He informed us that all of the panel concurred with that variation of approach.

As a result, on January 3, the same day, he sent out a revision—and this gets back, Mr. Chairman, to why the minutes probably were somewhat sparse on the actual telephone call on January 9—on January 3 he sent out a revision of the labeling and on January 5 he then sent out a memorandum confirming that a telephone conference call would be held and reminding them that the revision of page 43 had been distributed and would be further discussed at that time.

Therefore, before anything was received from Miles Laboratories on January 5, the question of labeling had been raised internally within FDA and had been discussed with the chairman and then with all members of the panel and had been set for discussion in the subsequent January 9 telephone call.

[Copies of these memorandums may be found in the appendix at pp. 351–352.]

Mr. DRINAN. One of the questions which has to be raised here, Mr. Hutt, is this: Under the statute we have to decide whether or not the advisory committee which has been established, whether its work could be performed by the agency itself.

In this case there is such an intermingling and intervention by the agency I am wondering whether that would be applicable.

I am making this comment thinking out loud as to the oversight function of this committee.

Mr. HUTT. Surely.

Mr. DRINAN. I yield back to the chairman.

Mr. HUTT. Father Drinan, if I may briefly advert to that. The major thing that the Food and Drug Administration does not have within its internal ranks are all of the experts available in the outside scientific world. We have good, sound, scientific people and administrators, and they do an excellent job. However, we have 17 panels here with seven experts each. That is a great many people.

We simply would not have those people within the Food and Drug Administration or the breadth of their expertise and experience. Therefore, I would suggest to you that we fully meet that statutory test; that is, that using FDA employees alone we could not have done this job.

Mr. DRINAN. When did you begin these advisory committees?

Mr. HUTT. On January 5, 1972.

Mr. DRINAN. FDA got along before somehow.

Mr. HUTT. Yes, and as we discussed both at the last hearing and in the hearing before, we had a major problem on our hands of 200,000 unregulated drugs on the market because we had not previously done something of this kind.

Mr. DRINAN. I yield back to the chairman.

Mr. FOUNTAIN. The December 22, 1972, memorandum signed by Gary L. Yingling was addressed to the antacid panel members and industry liaison. The first sentence reads as follows: "Enclosed you will find the final proposed draft report of the advisory review panel on over-the-counter antacid drugs." The last sentence of the memorandum reads, and I quote: "We will be calling you within the week to arrange a telephone conference call for the 1st or 2d week in January."

Why wasn't the consumer liaison on the panel provided a copy of the panel's December 22, 1972, draft report?

Mr. YINGLING. As I remember she was out of town during the mailing. She received a copy subsequently.

I am sure it was either sent to her or she came out to the office. I know she saw the copy and we went over it in some detail.

Mr. FOUNTAIN. I note from copies in the Miles folder that the December 22, 1972, Yingling memorandum and the panel's draft report were reprinted by the Proprietary Association. Can you tell me how that association got a copy of the draft report and your memorandum?

Mr. YINGLING. Yes. That was sent to Dr. Pisani, being one of the panel liaison members, who works for the Proprietary Association. It was sent to him at the Proprietary Association's address. That is how this association got a copy. They were the organization——

Mr. FOUNTAIN. He was the member of the panel representing them?

Mr. YINGLING. Yes.

Mr. HUTT. He was the nonvoting liaison representative.

Again, Mr. Chairman, the understanding was that the consumer and industry liaison could reproduce and distribute and receive comments back which would be considered during the telephone conversation on January 9. This was agreed to by the panel as a proper procedure.

Mr. FOUNTAIN. Of course, the consumer group did not get it, did they?

Mr. HUTT. It was available to her. She did get it and she did discuss it, as Mr. Yingling just stated, with FDA in some detail.

Mr. FOUNTAIN. Do you know when the consumer group or association got a copy of the draft report?

Mr. YINGLING. I cannot say. I am not sure of the exact date they received a copy.

Mr. FOUNTAIN. Do you have any record of that?

Mr. YINGLING. I am not sure that I do, sir.

Mr. HUTT. Mr. Chairman, obviously, as I stated earlier, in order to avoid any of these kinds of questions in the future we have already some months ago gone to a new procedure of putting it in the hearing clerk's office and giving 30 days notice in the Federal Register. This is one of the things we learned could be done better.

I think the new procedure is a much better one.

Mr. FOUNTAIN. How did Miles Laboratory get its copy of the report? From the Proprietary Association representative?

Mr. YINGLING. I assume so inasmuch as this copy has on it "From the Proprietary Association" stamped on the Xeroxed copy.

Mr. FOUNTAIN. The three-page January 3, 1973, memorandum that I have already placed in the record is unsigned. That memo, you will recall, is headed: "Notes for Presentation by the Commissioner to Dr. Ingelfinger," who was the panel chairman.

Mr. HUTT. To the best of my knowledge neither the Commissioner nor Dr. Ingelfinger ever saw this. We have attempted to find out whether the Commissioner ever talked to Dr. Ingelfinger.

To the best of our research that never happened.

Dr. GOLDBERG. Which Commissioner did you talk with?

Mr. HUTT. I am referring to Dr. Edwards. We are unable to find any record that he ever talked to Dr. Ingelfinger.

Mr. FOUNTAIN. In view of all the things which have transpired and about which there are no records, you are not in a position to say he did not see it or it did not reach him?

Mr. HUTT. I find the possibility of that to be extraordinarily remote.

Mr. Chairman, we could suggest that you call Dr. Ingelfinger and discuss that with him. I find it very difficult to imagine that that could have occurred.

Mr. FOUNTAIN. I have mixed emotions and some indecision at this point. I must say some serious questions are raised as to whether or not possible behind-the-scenes efforts were made to get the panel's draft report altered to suit the preferences of Miles Laboratories.

Mr. HUTT. Of course they were made but they were totally unsuccessful, after-the-fact, and amateurish.

Mr. FOUNTAIN. Was it proper for them to be made in this manner?

Mr. HUTT. In the Government, in a regulatory agency, we are approached constantly, constantly, with requests to do all kinds of things, by people in Congress, by people in the regulated industry, by consumer groups.

When people come in and talk to us and hand us a piece of paper like this, whoever it was handed to, we have little option but to look at it. We cannot say we will not look at any piece of paper whatever.

Once having looked at it I think you would agree it would have been highly improper for us to have destroyed it even though it was not shown to anyone else.

Therefore, Mr. Yingling did what was obviously the proper thing, to send it down to the files where it could be retained so that when Mr. Goldhammer looked through the files he quite properly found it.

However, from that fact alone to suggest that there was any impropriety it seems to me is a totally unwarranted and unfair suggestion.

I would suggest that it shows that what happened was entirely proper, that we did do our duty. When a citizen wishes to meet with us he has a right to do so. Our new procedural regulations make that clear, and I think any citizen and any Member of Congress would feel we do have an obligation of that type.

Second, we do not listen or take seriously submissions that late in the game which make suggestions that the Commissioner ought to call the chairman of the panel. That was not given by Mr. Yingling to the Commissioner. It was not distributed. It was simply filed away as it should have been.

To me just the opposite conclusion is drawn from the one you said might be drawn. I believe that it was handled properly.

Mr. FOUNTAIN. I am not talking about how you operated. Was it not the intention of the Miles Laboratory representative who prepared the memorandum for presentation to the Commissioner, that the Commissioner contact Dr. Ingelfinger?

Mr. HUTT. Yes, sir. Fortunately, to the best of our research, that never occurred and should not have occurred.

Mr. FOUNTAIN. I am not questioning the right of any firm adversely affected by a proposed regulation to seek to protect its interests. It

has a responsibility to its stockholders and the public in general to do so.

However, it should be pointed out that the OTC review procedures embodied in the regulations are intended to provide ample opportunity for comment by affected firms on proposed final monographs published in the Federal Register.

However, on January 3, 1973, a final proposed panel monograph had not yet been published nor even adopted. That is true; is it not?

Mr. HUTT. That is true, Mr. Chairman.

Again I trust you understand that I had described earlier the way that the panel itself had wanted this draft to receive fairly wide dissemination through the industry and consumer liaison so that anyone who was concerned about any particular aspect of it could get information back to the liaison member and those concerns could be raised in what later became the 3-hour telephone conversation on January 9.

It was entirely proper for the industry liaison to give this to Miles.

It was entirely proper for Miles to give its views back to the industry liaison and for the industry liaison to make those known at the time of the telephone conversation. That was the way the procedure was supposed to work.

What was improper was for Miles to make a suggestion that the Commissioner in some way meet with Dr. Ingelfinger and, as I say, we do not believe that that occurred. That would have been improper. That is why Mr. Yingling handled it as he did.

Mr. DRINAN. Why is it so proper the way Mr. Yingling handled it? It seems he should have handed this back to Miles Laboratories and said that the day of truth has come and gone. Sometime ago I wrote to a Federal agency on behalf of a constituent related to a banking matter and they quite properly sent my letter back and said they would not make it part of the file, this is ex parte, and they gave me a copy of the regulation.

The FCC has regulations like that. Why was it proper for him to do that? It seems it should have been returned and not even accepted as a document by the agency.

Mr. HUTT. Frankly, Father Drinan, that would concern me even more because we would then fail to have this document show up in our files as it should have so that Mr. Goldhammer could find it.

It seems to us that when someone tries to make——

Mr. DRINAN. You would have had less trouble.

Mr. HUTT. That is true, but we are not engaged in coverups. What we are trying to do is to maintain files that do contain everything that happens. This is something that happened.

It should not have happened, in my judgment. The company improperly made this overture.

Mr. DRINAN. When they make an improper overture, like a Federal judge and the FCC you should give it back.

Mr. HUTT. That is a matter of interpretation. It seems to me your rule is far more fraught with danger because people could make ex parte contacts and discuss things and then hand documents back and the record would never show what happened.

Mr. FOUNTAIN. Suppose they had done the same thing to a member of the panel? How would that have appeared?

Mr. HUTT. In my judgment I would have disqualified the member of the panel if it had reached a serious stage. If they simply made an overture, certainly the panel member should have told us. If there had been any discussion of substance, the panel member could not have voted thereafter.

Mr. DRINAN. Why does it not work in reverse? Why weren't you required to tell them?

Mr. HUTT. Because we were not voting, and during the discussion on the ninth it was my recollection for the very short time I was there that FDA, as was true, indeed, of all our discussions, was not saying, "We want you to do this" and "We are trying to persuade you to do that."

What we were doing was simply administering the panel, not attempting to influence its substantive decisions in any way. I do not think we did.

Mr. FOUNTAIN. Did you make the final decision regarding this, or did Dr. Schmidt make the final decision?

Mr. HUTT. He did. We know Dr. Schmidt never saw this. Dr. Crout, who also made that decision, never saw it.

Dr. GOLDBERG. Dr. Edwards made the final decision.

Mr. HUTT. Dr. Schmidt made the final decision on antacids.

Mr. FOUNTAIN. That is what he was talking about when he said he assumed full responsibility for it.

Mr. HUTT. That is correct.

Mr. FOUNTAIN. Let me now read a portion of the January 3, 1973, unsigned memorandum. Paragraphs 1 and 2 read as follows, and I quote:

1. It is essential—from the viewpoint of the FDA, Miles and the success of the entire O–T–C Review program—that the deficiencies in the current Draft Report with respect to Alka-Seltzer be remedied promptly. We hope that Dr. Edwards can, preferably by a personal meeting, impress this point on Dr. Ingelfinger. Although Dr. Edwards has the right, and indeed the obligation, to remedy errors in the Panel's proposal, it really makes more sense to try to have the Panel correct the problems itself.

2. In talking to Dr. Ingelfinger, Dr. Edwards should emphasize that the Antacid Panel has done a fine job in the main, for which he is grateful, but that it is essential that the Report be one that is defensible not only as an expression of the Panel's scientific opinion but also legally and as a proper approach to self medication. Unless the Report can be so defended, it will put the whole O–T–C program in jeopardy. Because of this overwhelmingly important consideration, Dr. Edwards is talking to Dr. Ingelfinger.

This last sentence appears to be significant, and I will repeat it: "Because of this overwhelmingly important consideration, Dr. Edwards is talking to Dr. Ingelfinger."

Mr. HUTT. That was what Miles wanted Dr. Edwards to do and which, of course, was rejected.

Mr. FOUNTAIN. But this suggests to me, Mr. Hutt, that Dr. Edwards was already talking to Dr.——

Mr. HUTT. No, Mr. Chairman. I think that is a misreading of this.

Mr. FOUNTAIN. I don't know how you misread it. It does not say "will" but it says "is."

Mr. HUTT. "Edwards should emphasize." Then they sum it up "Because of this problem that is why Dr. Edwards would be talking." It is clearly to be in the future.

Mr. FOUNTAIN. It is a justification for the conversation.

Mr. HUTT. That is right. There is absolutely no evidence that Dr. Edwards talked about this matter to Dr. Ingelfinger—at this time, prior to the press release announcing the report.

If you look under paragraph 3: "If feasible Dr. Edwards should ask Dr. Ingelfinger," et cetera. This is talking about what Miles would like Dr. Edwards to do.

Obviously Miles Laboratories would like the Food and Drug Administration and Dr. Edwards and Dr. Schmidt to do a lot of different things, none of which the agency or those two gentlemen were about to do or would have done.

Mr. FOUNTAIN. I would like to say that neither Miles Laboratories, nor any other firm, ought to ask FDA to do anything they did not think proper.

Mr. HUTT. I do not know what Miles Laboratories thought. It may well have thought this proper. In my judgment it was not proper but that is my judgment.

Mr. FOUNTAIN. The third paragraph of the memorandum summarizes the order of priority of the four areas of the report that Miles Laboratories felt must be remedied. It suggests that Dr. Edwards discuss all four areas with Dr. Ingelfinger. If that was not possible, Dr. Edwards was to cover the points of highest priority. The point of highest priority is as follows, and I quote: "First, the unjustified implication that Alka-Seltzer is unsafe should be eliminated. This means modifying the material at pages 43 and 45–46 of the draft report."

Were pages 43, 45, and 46 of the December 22, 1972, draft report modified by the panel as requested?

Mr. HUTT. Once again, let's go back. I stated earlier that 2 days or 3 days prior to this meeting at which this document was given, apparently to Dr. Novitch and Mr. Yingling—and again, Mr. Chairman, I do not recall being there, and it is possible I may have appeared for a moment or have been there for even longer—but 2 days prior to that a Food and Drug Administration employee, the panel administrator, had independently sought out Dr. Ingelfinger and had suggested changes on page 43, and indeed had sent out on that date, after talking to all members of the panel, some changes.

This was before Miles ever even raised the issue.

Mr. FOUNTAIN. They were changes which Miles suggested?

Mr. HUTT. I do not believe so.

Mr. YINGLING. No.

Mr. HUTT. I do not believe they were the changes Miles suggested; no.

Mr. FOUNTAIN. We will get to that.

The third paragraph also states:

> The simple fact here is that Miles has submitted valid studies showing the safety of its product and 40 years of extraordinary safety in use, and the panel has apparently disregarded these studies and relied on the Jennings letter and impressions relating to aspirin. Aside from the fact that this approach is legally indefensible, it is also scientifically wrong. Specifically, the reference to the Jennings letter should be deleted and the warnings and other aspersions presented in the draft report cannot be made applicable to Alka-Seltzer.

Was the reference to the Jennings letter deleted from the report?

Mr. HUTT. I do not know.

There is one other thing I would like to suggest, Mr. Chairman. The points that Miles was making here, as I mentioned earlier, they had every right to make to Dr. Pisani. The whole purpose of the telephone call of January 9 was so that the consumer and industry representative could report concerns raised by people outside the agency. So it is possible—and one would have to go through enormous detail to find out what happened—that some of these changes were made because Dr. Pisani raised them in the course of the January 9 telephone call and, in turn, the panel accepted those changes.

The fact they made the suggestion independently to us is totally irrelevant as to that because we did not follow through with this.

Mr. FOUNTAIN. I am not suggesting what was intended. I am simply putting on the record the facts as to what transpired.

Mr. HUTT. I would make this suggestion. If you would like us to we would go back and try to determine what requests were made by Dr. Pisani to the panel in the course of the January 9, telephone call and which ones mentioned in all of this material were in fact made.

Mr. YINGLING. I believe the quotation of the Jennings letter was taken out. In the Federal Register notice of April 5, Thursday, at page 8721, they cite "No. 4, Jennings, GH: Causal Influences in Haematemesis and Malaena, Gut 6: 1–13, 1965" takes care of his letter. That was a scientific journal and the real citation. The letter was only a letter to the editor.

Mr. FOUNTAIN. The Jennings letter was deleted from the report, then.

Mr. HUTT. Yes. We would have to see whether we can reconstruct——

Mr. FOUNTAIN. For whatever reason.

Mr. HUTT. We will have to reconstruct why the panel concluded to delete it.

Mr. FOUNTAIN. Paragraph 4 of the three-page unsigned memorandum in the folder reads as follows:

> Dr. Compton is talking to Dr. Edwards as doctor to doctor and as Miles' chief executive to the head of FDA. It is essential for each of them that these matters be corrected. Dr. Compton is not talking as a lawyer but should mention that from the viewpoint of his lawyers the bad treatment of Alka-Seltzer is legally indefensible.

Mr. HUTT. It sounds as if this was written by a lawyer.

Mr. FOUNTAIN. "The main point is that it should be corrected as a matter of sense and policy."

Is the Dr. Compton mentioned in this memorandum the same Dr. Compton who, in December 1972, was a member of FDA's National Drug Advisory Committee?

Mr. HUTT. He is to this day.

Mr. FOUNTAIN. One of the functions of the National Drug Advisory Committee in 1972 was to advise the Commissioner on FDA policy on drug enforcement matters. Is that right?

Mr. HUTT. Yes.

Mr. FOUNTAIN. The part of paragraph 4 I read suggested Dr. Compton, at the time the memorandum was written, was already talking to Dr. Edwards; does it not?

Mr. HUTT. No. It is the same kind of language saying he should talk to them.

What it is is a request.

Mr. FOUNTAIN. Giving him——

Mr. HUTT. That Dr. Edwards talk to Dr. Ingelfinger and take this kind of approach. That is why I characterized it earlier as somewhat humorous and naive.

Mr. FOUNTAIN. I know it is stated in the present tense, but you think he is suggesting that this was suggested conversation to be used.

Mr. HUTT. That is right.

Mr. FOUNTAIN. Do you know whether Dr. Compton did in fact talk to Dr. Edwards about these matters?

Mr. HUTT. I do not know. Again, we have looked through everything we can and we can find no suggestion of a discussion between Dr. Edwards and Dr. Ingelfinger.

As I did earlier, I would suggest that you talk to Dr. Ingelfinger about that.

I think I would point out here, and it is a shame Commissioner Schmidt had to leave, that the real issue is ultimately what conclusions came out of this entire affair.

As I said, Dr. Schmidt knew nothing of this until it came to light a week or two ago, which was the first time I remember seeing it myself.

Mr. FOUNTAIN. At least part of the issue is the procedures, which you say have been improved. These are things we are engaged in the process of determining.

Mr. HUTT. I agree. I would say, Mr. Chairman, if this were to occur again in the future my best judgment would be that the document should again be received and placed in the file as it was rather than looked at, discussed, and rejected. I believe very strongly that the administrative record in the agency should have everything in it and not be a somewhat incomplete file.

In that respect I would have to continue to disagree with Mr. Drinan because I think there would be enormous possibility for ex parte contacts which should not occur otherwise.

Dr. GOLDBERG. If you accept a document of that kind for your files, is not FDA under obligation to prepare a memorandum explaining the disposition of the document?

Mr. HUTT. Absolutely. There is no question about that. That should be done and there should be a file memorandum of the contact.

Our new procedural regulations make that absolutely clear. If this were to occur in the future this would be accompanied by a memorandum of the meeting.

Again we have come a long way in 3 years. I think our new procedures will do much to help out in this kind of situation.

Mr. FOUNTAIN. The fifth and last paragraph of the memorandum states:

> In a marked up copy of the Draft Report, Miles indicated the drafting changes which should be made. Miles is, of course, not wedded to this particular drafting and Dr. Compton can have his lawyers meeting with FDA people at any time to discuss the niceties of drafting. The important point, however, is that Dr. Edwards convince Dr. Ingelfinger of the desirability of making the changes in the Panel's Draft Report before it is submitted finally to the Commissioner.

Is this another situation where you feel Miles Laboratories was justified in getting Dr. Edwards to convince Dr. Ingelfinger of the desirability of changing the draft report before it was submitted finally to Dr. Edwards?

Mr. HUTT. I am sorry, sir. I think you misunderstood me. I never said they were justified in doing that. I said in my judgment it was improper, but once the contact was made we were obligated as a responsible administrative agency to keep a record of it, which we did.

Mr. FOUNTAIN. Can you explain why Miles Laboratories thought it was essential that Dr. Edwards convince Dr. Ingelfinger with regard to the change?

Mr. HUTT. They had a lot of money riding on it. Obviously one on the outside faced with effective regulatory action by the Food and Drug Administration will frequently use any kind of avenue to attempt to persuade us not to take that action.

As I have stated, the issue which really should be focused upon is what we did. Did we do the right thing in terms of the science and the law involved? I think here the record is totally clear that this issue followed proper procedure to begin with and we did not accept the invitation to engage in this kind of ex parte communication.

Second, the end result was based solely upon the administrative record and solely upon the scientific data and reasoning set out in the report.

I would request that the Commissioner have an opportunity to explain his reason for his scientific decision at some later date.

Mr. FOUNTAIN. We will give him that chance.

I believe you said FDA did not acknowledge receipt of the folder from Miles Laboratory nor reply to the requests contained therein?

Mr. HUTT. No, it was simply in the course of a meeting. It was handed apparently to Mr. Yingling and that was the end of it.

Mr. FOUNTAIN. Is that right, Mr. Yingling?

Mr. YINGLING. I do not follow.

Mr. FOUNTAIN. Did you reply to it?

Mr. YINGLING. No, sir. They went through the points they thought were important and we went through the document and listened.

Mr. FOUNTAIN. How long is that document?

Mr. YINGLING. The document is quite long. The appendixes B, C, and D were things they presented at the December 8 panel meeting.

Mr. FOUNTAIN. All the things they presented they had presented previously.

Mr. YINGLING. Yes.

Mr. HUTT. Actually the only, in a sense, impropriety, is the 3-page covering memorandum from which you have read.

I pointed out that the comments dated December 29, the memorandum of comments on the proposed draft, were solicited by the Proprietary Association and properly should have gone back to the Proprietary Association. I assume they did. I assume Dr. Pisani made those points at the telephone conversation on January 9 which was the proper thing to do.

He may have prevailed on some and not others. I simply do not know.

Mr. FOUNTAIN. All of these things might have been coincidental, or they might have been prompted by other sources, or by what the panel was in the process of doing anyway. However, we have to make the record.

Now I want to discuss the evidence of whether or not the panel's December 22, 1972, draft report was revised in accordance with Miles

Laboratories suggestions to eliminate the implications of possible lack of safety of Alka-Seltzer in the panel's report.

To facilitate a comparison of the original pages 43, 45, which Miles wanted altered in specific ways, I am placing into the record documents which established whether suggested revisions were made in the final order, again without saying whether they were made at Miles' suggestion or somebody else's suggestion.

In this connection the first document which I am placing in the record is page 43 of the panel's draft report with the Miles Laboratories' annotations.

[The material referred to follows:]

NOTE.—The first two paragraphs in Section I.D. have been rewritten in order more clearly to illustrate the insertions which are suggested to be made therein and which are underlined in blue ink. These insertions replace the phrase "a corrective for an antacid side effect" and are necessary in order for these paragraphs to conform to the language contained in page 50.[1]

d. Drugs combining antacid and other active ingredients

The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor *a corrective for an antacid side effect*, will contribute to the product's safety and effectiveness for use in antacid therapy alone. The addition of non-antacid or non-corrective ingredients may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor a *corrective for an antacid side effect* should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and non-antacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief of both of the active ingredients. The dual indication should clearly be stated on the label [and the label should include a prominently displayed warning that such a combination shall not be used for the treatment of heartburn and/or indigestion and/or sour stomach unless these symptoms are accompanied by indications for an analgesic.][2] Such a product is not appropriate for peptic ulcer and related * * *.

NOTE.—The use of Alka-Seltzer for upset stomach and symptoms which indicate the use of an analgesic is safe and effective. No such warning is appropriate.[3]

Mr. FOUNTAIN. This page concerns drugs combining antacid and other active ingredients.

D-1 of this page covers antacid and analgesic combinations for use when heartburn and/or indigestion and/or sour stomach are accompanied by indications for an analgesic. The panel's draft report stated:

The dual indication should clearly be stated on the label and the label should include a prominently displayed warning that such a combination shall not be used for the treatment of heartburn and/or indigestion and/or sour stomach unless these symptoms are accompanied by indications for an analgesic.

I emphasize that the panel wanted a "prominently displayed warning." In the annotation Miles Laboratories objected to the required warning saying "No such warning is appropriate" and supplied a revised page 43 which eliminated the requirement for a "prominently displayed warning."

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[1] Blue ink underlined portions in the original appear in italic.
[2] Bracketed material indicates portions crossed out in Miles Laboratories' submission.
[3] In the original submission, Miles Laboratories' "Notes" appear in the left hand margins next to the pertinent portions of the draft report.

The revised page 43 of Miles Laboratories is also being placed into the record.

[The material referred to follows:]

d. Drugs combining antacid and other active ingredients

The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor a corrective for an antacid side effect, will contribute to the product's safety and effectiveness for use in antacid therapy alone. The addition of non-antacid or noncorrective ingredients may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor a corrective for an antacid side effect should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and non-antacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief provided by both types of active ingredients. The indication section of the labeling should state clearly that the combination should be used only when heartburn and/or acid indigestion and/or sour stomach are accompanied by indications for an analgesic. Such a product is not appropriate for peptic ulcer and related * * *.

Mr. FOUNTAIN. To complete the picture, I am placing into the record page 8721 of the April 5, 1973, Federal Register [FR 38 No. 65, Part II]. This page is that part of the antacid panel's final report and proposed monograph which covers the subject matter on page 43 of the December 22, 1972, draft report.

[The material referred to follows. Emphasis added.]

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor a corrective for an antacid side effect should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and nonantacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product has concurrent symptoms which require the relief provided by both types of active ingredients. *The indication section of the labeling should state clearly that the combination should be used for heartburn and/or acid indigestion and/or sour stomach only when these symptoms are accompanied by indications for an analgesic.* Such a product is not appropriate for peptic ulcer and related disorders. Any analgesic ingredient that is generally recognized as safe and effective (see analgesic Monograph) may be used as the analgesic ingredient.

2. The Panel concludes that it is rational to include a nonantacid laxative ingredient in an antacid if the laxative is solely for the purpose of counteracting the constipating action of one or more of the antacid ingredients. Any laxative action ingredient that is generally recognized as safe and effective (see laxative Monograph) may be used as the laxative ingredient. No labeling claim for the laxative effect would be truthful, because the amount of nonantacid laxative ingredient present should not cause laxation, but only counteract the constipating effect of the antacid.

Comment. Any other combination of antacid with nonantacid active ingredients should be permitted by the Food and Drug Administration only after it is shown that the conditions for a combination drug set out in the regulations have been met. The Panel is unaware of any other such combinations which meet these conditions at the present time.

II. *Conditions under which antacid products are not generally recognized as safe and effective or are misbranded.* The use of antacids under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Panel concludes that the ingredients, labeling, and combination drugs involved should be removed from the market until scientific testing supports their use.

A. *Active ingredients.* No active ingredients for which data were submitted to the Panel and that is not included in Category I or Category III has, in the Panel's opinion, been shown by adequate and reliable scientific evidence to be safe and effective.

B. *Labeling.* The Panel concludes that it is not truthful and accurate to make claims or to use indications on the package label that the product may directly affect "nervous or emotional disturbances," "excessive smoking," "food intolerance," consumption of "alcoholic beverages," "acidosis," "nervous tension headaches," "cold symptoms," and "morning sickness of pregnancy" since the the relationship of such phenomena to gastric acidity is both unproven and unlikely.

C. *Drugs combining antacid and other active ingredients.* 1. Although the Panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for treatment of concurrent symptoms, *it concludes that fixed antacid-aspirin combinations are irrational for antacid use alone and therefore should not be labeled or marketed for such use. Not only are OTC antacids sometimes indiscriminately used, which may lead to aspirin toxicity with such combinations, but aspirin also has a potential for damaging the gastrointestinal mucosa by the topical action of breaking the mucosal barrier or by other mechanisms.*

In experiments in man and animals unbuffered aspirin causes greater visible gastric mucosal damage and more gastrointestinal blood loss than strongly buffered aspirin in solution, which causes little or none of these experimental forms of damage. *However, the actual clinical condition of major gastrointestinal hemorrhage associated with aspirin ingestion has been seen with both unbuffered and strongly buffered aspirin in solution. There is inadequate evidence to establish whether the risk of clinically major gastrointestinal hemorrhage is less with strongly buffered aspirin in solution than with unbuffered aspirin.* Because of this uncertainty and the lack of evidence of effectiveness of salicylate for antacid indications, benefit-risk considerations dictate that such a product not be indicated solely for antacid purposes.

Citations

(1) Brodie, D. A. and Chase, B. J.; "Role of Gastric Acid in Aspirin-Induced Gastric Irritation in the Rat," Gastroenterology, *53*:604–610, 1967.

(2) Brown, R. K. and Mitchell, N.; "The Influence of Some of the Salicyl Compounds (and alcoholic beverages) on the Natural History of Peptic Ulcer," Gastroenterology, *31*:198–203, 1956.

(3) Grossman, M. I.; Matsumoto, K. K.; Lichter, R. J.; "Fecal Blood Loss Produced by Oral and Intravenous Administration of Various Salicylates," Gastroenterology, *40*:383–388, 1961.

(4) *Jennings, G. H.; "Causal Influences in Haematemesis and Melaena," Gut, 6:1–13, 1965.*

(5) Langman, M. J. S.; "Epidemiological Evidence for the Association of Aspirin and Acute GI Bleeding," Gut, *11*:627–634, 1970.

(6) Leonards, J. R. and Levy, G.; "Reduction or Prevention of Aspirin-Induced Occult Gastrointestinal Blood Loss in Man," Clinical Pharmacology and Therapeutics, *10*:571–575, 1969.

(7) Thorsen, W. B. Jr.; Western, D.; Tanaka, Y. and Morrissey, J. F.; "Aspirin Injury to the Gastric Mucosa, Gastrocamera Observations of the Effect of pH," Archives of Internal Medicine, *121*:499–506, 1968.

2. The Panel concludes that it is not safe and effective concurrent therapy to add an anticholinergic ingredient to an OTC antacid product, because optimal use of antacids and anticholinergic drugs requires independent adjustment of dosages of each drug, because the addition of an anticholinergic drug in a concentration large enough to have detectable pharmacologic effects would result in a compound too toxic for use in self-medication, and because entirely safe amounts of anticholinergies have not been shown to affect gastric secretion or upper gastrointestinal symptoms. Since elderly persons number prominently among antacid users, cycloplegia and urinary retention induced by anticholinergic drugs is a definite risk. Thus, a fixed combination of antacid and anticholinergic will result, regardless of how formulated, in a mixture that is either unsafe or ineffective.

The same conclusions apply to combinations of antacids with sedative-hypnotic ingredients.

3. The Panel concludes that it is not rational concurrent therapy for a significant portion of the target population for the label to claim that a combination

product (e.g., mineral oil and magnesium hydroxide) is to be used both as an antacid and as a laxative if the laxative claim is supported by a nonantacid laxative ingredient.

The Panel recognizes that there are active antacid ingredients that may be effective as laxatives at higher doses than those used for antacid action. The Panel understands that the question whether such uses are appropriate will be reviewed by the Laxative Panel and, for this reason, takes no position on use of these ingredients as laxatives.

4. The Panel is not aware of any study showing that the addition of an antipeptic agent to an antacid product increases the product's efficacy as an antacid or is otherwise effective as a means of managing upper gastrointestinal symptoms. All antacids are antipeptic in the sense that peptic activity is reduced as pH increases and pepsin is irreversibly inactivated at pH's above 7. No claim for antipeptic activity can be considered truthful and accurate until it is substantiated both by scientifically valid in vitro tests showing that the antipeptic action is substantially greater than that of an agent with only antacid action (such as sodium bicarbonate), and it is proved by studies that the antipeptic activity is clinically meaningful and therefore contributes to the product's effectiveness.

5. The Panel concludes that the addition of proteolytic agents or bile or bile salts to antacid products is unsafe. Since pepsin is presumably involved in the pathogenesis of peptic ulcer, the addition of pepsin to antacid products may be potentially harmful. Since bile and bile salts can damage gastric mucosa, and since they may be involved in the pathogenesis of gastric ulcer, these substances should not be permitted in antacid products.

6. The Panel concludes that the addition of an antiemetic to an antacid product is not rational therapy for a significant portion of the target population.

Mr. FOUNTAIN. It is apparent from D–1 in the Federal Register that the wording suggested by Miles Laboratories in its revised page 43 was adopted by FDA virtually unchanged, thereby eliminating the warning the panel had required at page 43 of its December 22, 1972, draft report.

Mr. HUTT. Mr. Chairman, I do not think that is accurate.

Mr. Welch sent out revised language to the panel after discussing revised language with the panel by telephone on January 3, 2 days before the date on which FDA received this document.

That revised language, it is my recollection, is basically the language of the final report, not the Miles language at all.

Mr. FOUNTAIN. But it is also the same language which Miles recommended.

Mr. HUTT. No; that is not true.

Dr. NOVITCH. Mr. Chairman, the original draft, the December 22 draft, states:

> The panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief of both active ingredients. The dual indication should clearly be stated on the label.

Then crossed out on the Miles draft is:

> And the label should include a prominently displayed warning that such a combination shall not be used for the treatment of heartburn and/or indigestion and/or sour stomach unless these symptoms are accompanied by indications for an analgesic.

The final report and the draft which was sent out to the panel——

Mr. HUTT. This is the January 3, 1973, draft by Mr. Welch.

Dr. NOVITCH. It states:

> The indication section of the labeling should state clearly that the combination should be used only when heartburn and/or acid ingestion and/or sour stomach are accompanied by indications for analgesic.

In other words, it is virtually the same language as in the draft of December 22 with the exception that the warning was changed to a clear, limited indication for concurrent use.

That is quite different from the Miles suggestion.

Mr. FOUNTAIN. Was that partly what Miles suggested?

Dr. NOVITCH. No.

Mr. HUTT. It was quite different. The idea of Miles was to eliminate either a warning or any kind of a link and independently, as I mentioned, Mr. Welch, who has no recollection of ever having seen this document at any time, had come up with his recommendation that the panel should consider this alternative and had called the panel and received their concurrence in that approach.

Mr. FOUNTAIN. Mr. Goldhammer, my question was based on information I received from you, based upon a thorough reading of the record. What is your response to the statements just made?

Mr. GOLDHAMMER. Page 43, as originally prepared for distribution, presumably by FDA for the panel, reflects, as the evidence here indicates, what transpired at the panel's meeting on December 8 and 9. This reads as follows at page 43 of the panel's draft report sent out on December 22:

> If antacid combinations are to be allowed the use of the combination of an antacid and an active ingredient that is neither an antacid nor a corrective for an antacid side effect should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and nonantacid ingredient. This dual indication should be clearly stated on the product label:
>
> One, the panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief of both of the active ingredients. The dual indication should clearly be stated on the label and the label should include a prominently displayed warning that such a combination shall not be used for the treatment of heartburn and/or indigestion and/or sour stomach unless these symptoms are accompanied by indications for an analgesic.

The annotation of Miles adjoining the requirement for a prominently displayed warning states:

> NOTE.—The use of Alka-Seltzer for upset stomach and symptoms which indicate the use of an analgesic is safe and effective. No such warning is appropriate.

They submitted a revised page 43 which is precisely the same as the old unrevised page 43, except for that portion which relates to the requirement for a prominently displayed warning.

The revised page 43——

Dr. NOVITCH. Revised by Miles?

Mr. GOLDHAMMER. Revised by Miles. You will find it in the submission presented on January 5.

Mr. HUTT. That is the old page 43 with crossouts on it.

Mr. GOLDHAMMER. Mine does not have crossouts.

Mr. THOMPSON. This one does. You gave this to me.

Mr. GOLDHAMMER. I would not say that is crossed out.

Mr. HUTT. Wait a moment. Could we see your document? You may have the wrong document.

Mr. GOLDHAMMER. Let me explain what I have here. Before you come up here, Mr. Hutt, will you let me explain what I have here?

This is the submission which was made on January 5 by Miles to FDA. That submission has a 3-page memorandum containing the comments Dr. Edwards should make to Dr. Ingelfinger.

Then there was a 7- or 8-page memorandum which went into detail and was signed by the general counsel of Miles Laboratories.

Then there was a letter from Mr. Yingling to the members of the panel and industry liaison dated December 22, 1972, which indicated that the draft report of December 22, 1972, was being distributed, and there would be a telephone conference at some time in the near future.

Then there was the copy of a draft report.

This page 43 and that copy of the draft report was in the black folder given to Mr. Yingling on January 5, 1973.

Now, Mr. Hutt——

Mr. HUTT. The only page 43 we have, Mr. Goldhammer, is a document which has a note at the top and has various things underlined and crossed out.

Mr. GOLDHAMMER. That is the same thing. I see no crossout here.

Mr. HUTT. It is a crossout. If you look down at the bottom where it starts "The dual indication should clearly be stated on the label," they put a period and crossed out the rest.

Mr. YINGLING. It is crossed out in red pencil. I don't know how it would copy.

Mr. GOLDHAMMER. It is not shown here.

Mr. FOUNTAIN. The first four words are crossed out, "dual indication," and so on. The paper looks as though there was a line. The rest does not show up.

Mr. HUTT. That is right. The company asked that all that be crossed out. That is the only page 43 that was given to us.

Mr. GOLDHAMMER. In the draft report which went out to the members on December 22, was that crossed out?

Mr. YINGLING. December what?

Mr. GOLDHAMMER. December 22.

Mr. YINGLING. No, sir.

Mr. GOLDHAMMER. It was not?

Mr. YINGLING. No, sir.

Mr. GOLDHAMMER. The only thing I can say, then, is that when Miles Laboratories put this notation that no such warning is necessary, they crossed that portion out, and then—and you should have this—they submitted in its place a new page 43 labeled "Revised 43."

Mr. THOMPSON. Excuse me.

Mr. HUTT. They did not submit that. That is where the confusion has arisen.

Mr. THOMPSON. What was the date those documents were received by Mr. Yingling?

Mr. YINGLING. January 5.

Mr. THOMPSON. According to what you gave me I have revised January 3, 1973.

Mr. GOLDHAMMER. That is the date of the first memorandum in that packet of material given on the 5th of January. You have that there. It is dated January 3.

Mr. FOUNTAIN. Why not observe their copy and let them see yours.

Mr. HUTT. We do not have that in what was submitted on the date you mention, in the black volume here.

Mr. FOUNTAIN. The revised sheets?

Mr. HUTT. We do not have the page you refer to. I do not know where you got it.

Mr. GOLDHAMMER. This was in that material.

Mr. YINGLING. Was the revised page 43 stuck loosely in the volume or was it bound in the volume as the rest of the material?

Mr. GOLDHAMMER. It was secured in the volume with the rest of the material. They were submitting a revised page 43.

Mr. HUTT. The revised 43 that you are looking at is our revision of 2 or 3 days earlier which was sent out to the panel with Mr. Welch's memorandum of January 3.

What I think happened is that you got hold of a page that we revised, not the page that Miles revised.

What the panel adopted was Armond Welch's revision which had been sent out on January 3. They rejected the revision suggested by Miles Laboratories.

Mr. GOLDHAMMER. This will have to be resolved.

Mr. FOUNTAIN. In the interest of time I suggest you get together to see whether you can resolve this question so the record will be completely clear.

Mr. THOMPSON. If I might make one point, Mr. Chairman, The materials that Mr. Goldhammer provided me show that lines were drawn through every one of the bottom four lines.

If that, indeed, was the recommendation submitted to FDA by Miles it bears no resemblance to what they ultimately came out with.

Mr. FOUNTAIN. FDA says there is a revised sheet.

Mr. HUTT. That revision, Mr. Chairman, was the one prepared by an FDA employee, the administrator of the panel, after discussing the issue on January 3 with Dr. Ingelfinger and the members of his panel.

Mr. FOUNTAIN. Was that in the same volume?

Mr. YINGLING. When I got the document back, sir, after Mr. Goldhammer called me——

Mr. FOUNTAIN. The Miles document?

Mr. YINGLING. Yes. When I got the document back after Mr. Goldhammer called me and went to the office where it was located and where he was looking at it, I found in there a revision dated January 3, 1973, of page 43 and a revision dated January 8, 1973, of page 22 dealing with the aluminum statement.

Both of these pages were just loosely stuck in the document. They were not punched as the rest of the documents were. They did not, as it appears to me, come with the rest of the document.

I would not normally file loose papers in the middle of a bound document. I would have stapled them on the front and put a note there.

I would not have taken a bound volume and left loose papers in it.

Mr. FOUNTAIN. This is your own revision?

Mr. YINGLING. Yes.

Mr. HUTT. Our copy has no punchmarks in it.

Mr. FOUNTAIN. Why would you put your own revision in somebody else's document?

Mr. YINGLING. I don't know when it occurred.

Mr. HUTT. It could have occurred at any time.

Mr. YINGLING. I don't know how they got there. I would have assumed Mr. Goldhammer put them in there, honestly.

Mr. GOLDHAMMER. You think I put that in?

Mr. YINGLING. Honestly.

Mr. HUTT. We have no idea.

Mr. FOUNTAIN. You are suggesting Mr. Goldhammer manufactured this?

Mr. HUTT. No, no. Absolutely not.

Mr. YINGLING. No.

Mr. HUTT. There was no suggestion of that, Mr. Chairman.

Mr. YINGLING. Mr. Goldhammer reviewed the document, called me on the phone, asked me about the document.

I went upstairs and found the bound document and two loose pages—43 and 22.

I assumed while he looked through the document he had been comparing pages and left two pages in there.

Mr. FOUNTAIN. Mr. Goldhammer, how did you get the pages you have?

Mr. GOLDHAMMER. What I did was this: I had asked FDA to have specific pages copied. I did not ask them to copy the entire document.

I selected those pages which suggested changes because I was curious to know whether those requested changes had actually been granted.

I put clips on the pages I wanted copied, and this is what I got back from FDA.

Mr. HUTT. This may forever remain a mystery. However, to summarize, the final version adopted by the panel was the version drafted by Mr. Welch some time before the 3d of January and which he discussed by telephone with the panel, with all members of the panel on the 3d of January, and which he then sent out with his memorandum of January 3 entitled "From Panel Administrator to Antacid Panel Members and Consultants, Subject: Page 43 Revision."

I have redrafted paragraph 1 of this page. The proposed revision has been discussed with Dr. Ingelfinger and will be discussed further in a conference call scheduled for January 9. Armond Welch.

It went to everyone.

Mr. FOUNTAIN. I am now placing in the record pages 45 and 46 of the panel's December 22, 1972, draft report containing the Miles Laboratory annotations.

[The material referred to follows:]

II. Conditions under which antacid products are not generally recognized as safe and effective or are misbranded

The use of antacids under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Panel concludes that the ingredients, labeling, and combination drugs involved should be removed from the market until scientific testing supports their use.

A. Active ingredients

No active ingredient for which [——— [1]] not included in Category I or Category III has, in the Panel's opinion, been shown by adequate and reliable scientific evidence to be safe and effective.

B. Labeling

The Panel concludes that it is not truthful and accurate to make claims or to use indications on the package label that the product may directly affect "nervous or

[1] Handwritten notation not legible.

emotional disturbances", "excessive smoking", "food intolerance", consumption of "alcoholic beverages", "acidosis", "nervous tension headaches", "cold symptoms", and "morning sickness of pregnancy" since the relationship of such phenomena to gastric acidity is both unproven and unlikely.

C. Drugs combining antacid and other active ingredients

1. Although the panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for concurrent symptoms, it concludes that fixed antacid-aspirin combinations are irrational for antacid use alone and therefore should not be labeled or marketed for such use. Not only are OTC antacids sometimes indiscriminately used, which may lead to aspirin toxicity with such combinations, but aspirin also has a potential for damaging the gastrointestinal mucosa by the topical action of breaking the mucosal barrier or by other mechanisms.

NOTE.—The italicized portion of section II.C.1 exhibits confusion between the reaction mixture of Alka-Seltzer and the dry ingredients from which the tablet is made. This paragraph should not apply to Alka-Seltzer. It fails to differentiate aspirin from a buffered solution of sodium acetylsalicylate. The underlined portion is only appropriate to the degree that it relates to a solid mixture of an antacid and aspirin in its acid form intended to be taken as such. It does not appropriately apply to all (for reasons already stated and supported by data submitted to the Panel) in referring to a reaction mixture containing the water soluble wholly dissolved sodium acetylsalicylate in a buffered solution.

CITATIONS

(1) Brodie, DA and Chase, BJ; "Role of Gastric Acid In Aspirin-Induced Gastric Irritation In The Rat", Gastroenterology, 53:604–610, 1967.

(2) Grossman, MI; Matsumoto, KK; Lichter, RJ; "Fecal Blood Loss Produced By Oral and Intravenous Administration of Various Salicylates", Gastroenterology, 40:383–388, 1961.

(3) *Jennings, GH; "Alka-Seltzer and Haematemesis", Letter to the Editor; Brit. Med. J., 16:475, 1963.*[2]

Note: Delete Jennings citation. See memorandum comment.[2] * * *

Mr. FOUNTAIN. At page 46 the panel had listed three citations supporting its position, citation 3 being:

Jennings, GH; "Alka-Seltzer and Haematemesis," Letter to the Editor; Brit. Med. J., 16:475, 1963.

Miles Laboratories' annotation 3 reads as follows:

"Note: Delete Jennings citation. See memorandum comments."

Reference has already been made to that. Nobody knows who deleted it.

The page has an arrow pointing to citation 3 with the word "out" written above.

Was the word "out" written by someone in FDA?

Mr. YINGLING. That is my writing.

Mr. FOUNTAIN. The panel's final report published at page 8721 of the April 5, 1973, Federal Register, which already is in the record, indicates that citation 3, the Jennings letter, was in fact deleted, and——

Mr. HUTT. Again that is a misleading statement. Citation No. 4, as published in the Federal Register, was another Jennings article on the precise same subject which covered apparently everything in the initial letter to the editor.

In addition the panel added four more citations.

Mr. YINGLING. The Jennings letter was replaced because the Gut cite was involved—that is the name of a journal, Mr. Chairman.

Mr. FOUNTAIN. At page 45——

Dr. NOVITCH. One moment, please, Mr. Chairman.

Mr. FOUNTAIN. Yes.

Mr. HUTT. I think we should point out, Mr. Chairman, that other recommendations made by Miles for deletion of material were rejected.

[2] At this "note" appears a handwritten arrow with the word "out" pointed to the Jennings citation 3.

Mr. FOUNTAIN. You might submit those for the record so we will know what they are.

Mr. HUTT. Surely. The sentence on page 45 which reads:

> Although the panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for concurrent symptoms, it concludes that fixed antacid/aspirin combinations are irrational for antacid use alone.

Et cetera.

Miles argued that should be deleted very, very strongly and they did not prevail.

Indeed, as you are aware, not only did they not prevail at that stage but the final monograph contains roughly the same language, and we are taking that position today.

Mr. FOUNTAIN. My questions are designed to bring that out.

At page 45 of the draft report Miles Laboratories inserted an annotation contending that Alka-Seltzer is taken as a buffered solution and therefore is not subject to the panel's comments in section II. C. 1, page 46, on aspirin toxicity and the capacity of aspirin to damage the gastrointestinal mucosa.

However, the final version of II. C. at page 8721 of the April 5, 1973, Federal Register was not changed.

Instead the panel amplified it to include a statement stressing the possibility of hazard from strongly buffered aspirin solutions.

But on June 4, 1974, more than a year later, in an order published in the Federal Register, FDA did not accept the panel's statement of the potential hazard of Alka-Seltzer solution and stated instead in the final regulation, at page 19875 the following:

> An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

I am placing page 19875 of the June 4, 1974, Federal Register into the record.

[The material referred to follows:]

* * * * * * *

(c) Bismuth-containing active ingredients:
(1) Bismuth aluminate.
(2) Bismuth carbonate.
(3) Bismuth subcarbonate.
(4) Bismuth subgallate.
(5) Bismuth subnitrate.
(d) Calcium-containing active ingredients: Calcium, as carbonate or phosphate; maximum daily dosage limit 160 mEq. calcium (e.g. 8 grams calcium carbonate).
(e) Citrate-containing active ingredients: Citrate ion, as citric acid or salt; maximum daily dosage limit 8 grams.
(f) Glycine (aminoacetic acid).
(g) Magnesium-containing active ingredients:
(1) Hydrate magnesium aluminate activated sulfate.
(2) Magaldrate.
(3) Magnesium aluminosilicates.
(4) Magnesium carbonate.
(5) Magnesium glycinate.
(6) Magnesium hydroxide.
(7) Magnesium oxide.
(8) Magnesium trisilicate.
(h) Milk solids, dried.

(i) Phosphate-containing active ingredients:
(1) Aluminum phosphate; maximum daily dosage limit 8 grams.
(2) Mono or dibasic calcium salt; maximum daily dosage limit 2 grams.
(3) Tricalcium phosphate; maximum daily dosage limit 24 grams.
(j) Potassium-containing active ingredients:
(1) Potassium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older.
(2) Sodium potassium tartrate.
(k) Sodium-containing active ingredients:
(1) Sodium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of sodium for persons up to 60 years old and 300 mEq. of sodium for persons 60 years or older. and 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older. The warning required by § 330.1(g) concerning overdoses is not required on a product containing only sodium bicarbonate powder.
(2) Sodium potassium tartrate.
(l) Silicates:
(1) Magnesium aluminosilicates.
(2) Magnesium trisilicate.
(m) Tartrate-containing active ingredients. Tartaric acid or its salts; Maximum daily dosage limit 400 mEq. (15 grams) of tartrate.

§ *331.15 Combination with nonantacid active ingredients.*

(a) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient to correct for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.
(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.
(c) An antacid may contain any generally recognized as safe and effective antiflatulent ingredient if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

SUBPART C—TESTING PROCEDURES

§ *331.20 Apparatus and reagents.*

(a) pH meter, equipped with glass and saturated calomel electrodes.
(b) Magnetic stirrer.
(c) Magnetic stirring bars (about 40 mm. long and 10 mm. in diameter).
(d) 50 ml. buret.
(e) Buret stand.
(f) 100 ml. beakers.
(g) 250 ml. beakers.
(h) 10 ml., 20 ml. and 30 ml. pipets calibrated to deliver.
(i) Tablet comminuting device.
(j) A number 20 and 100 U.S. standard mesh sieve.
(k) Tablet disintegration apparatus.
(l) 0.1 N, 0.5 N and 1.0 N hydrochlorlic acid.
(m) 0.5 N sodium hydroxide.
(n) Standard pH 4.0 buffer solution (0.05 M potassium hydrogen phthalate)
(o) 95 percent ethanol.
(p) Distilled Water.

§ *331.21 Determination of percent contribution of active ingredients.*

To determine the percent contribution of an antacid active ingredient, place an accurately weighed amount of the antacid active ingredient equal to the amount present in a unit dose of the product into a 250 ml. beaker. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix thoroughly to wet the sample (ethanol may affect the acid neutralizing capacity). Add water to a volume of 70 ml. and mix on magnetic stirrer at 300±30 r.p.m. for about one minute. Analyze the sample according to the prodecure set forth in § 331.20 and calculate

the percent contribution of the antacid active ingredient in the total product as follows:

$$\text{Percent contribution} = \frac{\text{Total mEq. Antacid Active Ingredient} \times 100}{\text{Total mEq. Antacid Product}}$$

§ 331.22 *Reagent standardization.*

Standardize the sodium hydroxide (NaOH) and Hydrochloric acid (HCl) solutions according to the procedures in the United States Pharmacopeia XVIII (NaOH page 1036 and HCl page 1034) or the Official Methods of Analysis of the Association of Official Analytical Chemists, 11th Ed., 1970, (NaOH page 876 and HCl page 873).[1]

§ 331.23 *Temperature standardization.*

All tests shall be conducted at 25° C ± 3°.

§ 331.24 *Tablet disintegration test.*

A tablet disintegration test shall be performed on tablets that are not to be chewed following the procedures described in the United States Pharmacopeia XVIII (page 932). If the label states the tablet may be swallowed, it must disintegrate within a 10-minute time limit pursuant to the test procedure using simulated gastric fluid test solution without enzymes, the United States Pharmacopeia XVIII page 1026, rather than water as the immersion fluid.

§ 331.25 *Preliminary antacid test.*

(a) *pH meter.* Standardize the pH meter at pH 4.0 with the standardizing buffer and check for proper operation at pH 1 with 0.1 N HCl.

(b) *Dosage form testing.* (1) *Liquid sample.* Place an accurately weighed (calculate density) and well mixed amount of the antacid product equivalent to the minimum labeled dosage; e.g., 5 ml., into a 100 ml. beaker. Add sufficient water to obtain a total volume of about 40 ml. and mix on magnetic stirrer at 300 ± 30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.25.

(2) *Chewable and rapidly soluble tablet sample.* Place an accurately weighed amount of a tablet composite equivalent to the minimum labeled dosage into a 100 ml. beaker. (The composite shall be prepared by determining the average weight of not less than 20 tablets and then comminuting the tablets sufficiently to pass through a number 20 U.S. standard mesh sieve and held by a number 100 U.S. standard mesh sieve.) Mix the sieved material to obtain a uniform sample. If wetting is desired, add no more than 5 ml. of 95 percent ethanol and mix to wet the sample thoroughly (ethanol may effect the acid neutralizing capacity). Add water to a volume of 40 ml. and mix on magnetic stirrer at 300 ± 30 r.p.m. for about one minute. (Capsules should be tested in the same manner using the sieved capsule powder as the sample.) Analyze the sample according to the procedure set forth in § 331.25.

* * * * * * *

Mr. FOUNTAIN. Based on documents placed in the record, and based upon the briefing I have had, it would appear that the changes requested by Miles Laboratories were granted insofar as Alka-Seltzer's safety is concerned. Is that right?

Mr. HUTT. I do not believe so. Perhaps I am missing the thrust of the question.

They wanted a statement made about safety. That was rejected by the panel in the January 9 telephone conversation. It must have been rejected. I do not see any change.

Mr. FOUNTAIN. Here again I am advised by Mr. Goldhammer that the request by Miles Laboratories were granted in full concerning Alka-Seltzer.

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[1] Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, D.C. 20044.

Mr. HUTT. Mr. Goldhammer, could you explain——

Mr. FOUNTAIN. Granted by FDA.

Mr. HUTT. You mean in the final order?

Mr. FOUNTAIN. Yes; the final order is what I am talking about.

Mr. HUTT. I will have to check that. You were reading from——

Mr. FOUNTAIN. What went into the Federal Register, June 4, 1974.

Mr. HUTT. You were reading from the panel report and proposal. Then you were reading from the final order, from the regulation in the final order?

Mr. FOUNTAIN. Yes.

Mr. HUTT. There was no change in the final order from the proposal in terms of the monograph. There was no change whatever. I will get the proposed regulation language and the final order regulation language. They say the same thing.

On page 8724, in the April 5, 1973, Federal Register, paragraph *g(2)*, right-hand column, halfway down, "Combination with nonantacid active ingredients:" "An antacid may contain any generally recognized safe and effective analgesic ingredients—see analgesic monograph—if it is indicated for use solely for the concurrent symptoms involved, for example, headache and acid indigestion."

If you look at the portion of the page you just read, Mr. Chairman, section 331.15(b) page 19875, June 4, 1974, Federal Register, it states the identical thing, except that it adds "and is marketed in a form intended for ingestion as a solution." That was an inadvertent omission the first time around in the proposal.

Therefore, the answer that the request by Miles—the Food and Drug Administration did not in any way alter the panel's conclusions from the proposal through the final order through today.

[See appendix, pp. 354–363 for FDA submission on this matter.]

Mr. FOUNTAIN. Which proposal?

Mr. HUTT. The proposal of April 5, 1973, which was the result of the January 9 telephone call.

Mr. FOUNTAIN. And after Miles Laboratories had made its suggestions?

Mr. HUTT. After the panel had held its final telephone conversation, its final meeting by telephone on January 9, 1973.

The recommendation for regulatory language that was made to the Commissioner of Food and Drugs at that time is essentially identical, and certainly in practical terms has the identical legal and scientific effect, as the monograph which was finally adopted by the Commissioner of Food and Drugs.

Mr. FOUNTAIN. They did contain a number of the suggestions made by Miles Laboratories even though they might have been made by somebody else, also.

Mr. HUTT. I am sorry, Mr. Chairman. I do not believe that is true. No.

The Miles Laboratories suggestion was rejected.

Mr. FOUNTAIN. What is your comment on that, Mr. Goldhammer?

Mr. GOLDHAMMER. Miles wanted the warning removed. It was removed.

FDA might have done it independently, but Miles said the warning was not necessary for Alka-Seltzer.

Mr. HUTT. The warning was restated with the concurrence of the panel as a limited indication as I discussed before, Mr. Goldhammer.

What I was trying to point out was that from the time of the final report of the panel through the final Commissioner's conclusion on the monograph there was no change.

I thought that was what we were discussing.

Mr. GOLDHAMMER. What we had was the December 22, 1972, draft report. That draft report very clearly said that there was to be a warning, a conspicuously labeled warning.

Miles Laboratory objected and said it was not necessary. When I asked FDA for certain documents to be reprinted from Miles' submission, there was given to me by FDA, attached to page 43, a revised page 43.

Mr. HUTT. Yes.

Mr. GOLDHAMMER. You have given us a different explanation. There was nothing at the time I got this copy from FDA to indicate that it was not part of the Miles' submission.

Mr. HUTT. That may have been an error at the time that you were given that document.

Mr. GOLDHAMMER. It was in that packet of material from the Miles' submission I had requested. I cannot at this time recall whether it was attached through clips, punch holes, or whether it was loose. I do not remember.

However, I put a clip at each page I wanted duplicated by FDA, and this came with that material.

The fact is that the request of Miles for a deletion of the warning actually took place.

Mr. HUTT. No.

Mr. GOLDHAMMER. Whatever happened——

Mr. HUTT. The fact is that Miles came in and requested something after a different thing had taken place. Miles to the best of my knowledge never concurred, and indeed objected to the linked indication, I am informed, during the telephone conversation of January 9. The panel did not adopt their position.

Mr. GOLDHAMMER. I am not describing how it came about that the changes were made. I am merely saying the request was made, and in the final report the objection to the warning was no longer necessary because the labeling declaration was no longer in the form of a warning.

I am not saying how that came about. I am simply relating the changes made to those Miles requested.

No. 2, Miles requested that there be deleted reference to the Jennings letter.

At that request appears the word "out." Mr. Yingling said he put that word there.

Mr. YINGLING. Yes, sir.

Mr. GOLDHAMMER. The fact is that the order does not contain a reference to the Jennings letter. We have observed that there was a different Jennings article cited. A copy of each will go into the record and will be there for the public to see.

[The documents referred to follow:]

[From the British Medical Journal of Feb. 16, 1963]

"ALKA-SELTZER" AND HAEMATEMESIS

Sir: May I support Dr. A. C. Arthur's views on "alka-seltzer" tablets (January 26, p. 260) as a cause of bleeding from the stomach. I have recently been reviewing my cases of gastro-intestinal bleeding and I find that in just over two years, from the end of 1958, I saw 134 such cases due to aspirin-containing preparations. Of these, twenty-four subjects had very recently taken alka-seltzer and nineteen had not taken any other salicylate except alka-seltzer, which had often been taken in small doses of one or two tablets.

The advertisement of such tablets as giving relief from stomach upsets is in my opinion morally wrong, since it is in subjects of these disorders that aspirin is most prone to cause haemorrhage. If such advertising cannot be prevented then at least the fact that the advertised tablets contain aspirin should be made evident to all. Most of my patients were ignorant of this fact.

The trade names of many aspirin-containing preparations: "anadin," "antoin," "Beecham's powders," "macprin" and "solprin," to name only a few, do not reveal to the uninitiated their aspirin content. All these preparations feature in the immediate antecedent history of haematemesis in my list of cases.—I am, etc.,

G. H. JENNINGS,
Edgware General Hospital,
Edgware, Middlesex.

[Gut, 6:1-13, 1965]

CAUSAL INFLUENCES IN HAEMATEMESIS AND MELAENA

(By G. H. Jennings, Edgware General Hospital, Middlesex)

EDITORIAL SYNOPSIS

"The gun must be loaded in order for an explosion to occur when salicylates pull the trigger" (Grossman, Matsumoto, and Lichter, 1961). This study substantiates this aphorism. The series of cases particularly emphasizes the importance of extrinsic factors, such as excessive emotion, fatigue, anxiety, infection, alcohol, irregular meals, and heavy smoking, which may contribute singly or jointly to a bleeding episode.

The official figures have in recent years shown an increasing incidence of peptic ulcer, and particularly of chronic duodenal ulcer, in both sexes (Avery Jones, 1957). It does not seem likely that this large increase can be ascribed to intrinsic constitutional factors (familial tendency, age, sex, blood group) and to discover its cause external circumstances need to be considered.

One of the striking ways in which the increased incidence of ulcer is seen in the wards of a general hospital is in the large number of cases of haematemesis and melaena admitted, and it was felt that by careful consideration of such cases of bleeding ulcer some clues might be obtained as to the causes of the total increase in incidence and in particular as to the nature of any deleterious external influences.

MATERIAL

The patients were those admitted to the general wards of the hospital and were consecutive during four years (1958–61 inclusive). The wards to which they were admitted were equal-sized male and female units with a total of 70 beds under the care of the writer and all the patients were questioned and examined by him soon after admission.

The area from which they came is one of the very large suburban areas characteristic of modern city development and its population is a mixed one with a predominance of business men and tradespeople, many of the former commuting daily to London; there is also a fair sprinkling of professional men. The area is generally prosperous, with a moderate number of factories and light engineering premises. Two or three of the districts are of lesser affluence but there was little unemployment in the area during the time of the survey.

In this period 321 cases were considered with 338 admissions for haemorrhage, 16 patients being admitted twice and one three times. The types of case are shown in Table I in which the age and sex distribution can also be seen. A total of 244 men and 93 women were admitted, 227 men and 87 women being ulcer cases. Of the 314 admissions for ulcer in the series, 172 were classified as acute and 142 as chronic. The diagnosis was made as between acute and chronic ulcers on historical and radiological evidence, and while this is not completely accurate it was felt to be reasonably reliable. Most of the patients were in hospital for about four to five weeks from the onset of the haemorrhage and they were radiographed at the end of this period. Those who had no ulcer crater visible on the radiograph, or who merely showed mucosal changes or duodenal irritability, were classified as acute. At first those with duodenal irritability, of which there were 28, were classified as acute duodenal ulcers, but this was later considered an uncertain division and has been excluded from the account. Historical evidence, in general, supported the radiological findings, being of none or brief and uncharacteristic previous dyspepsia in the radiologically negative cases. The incidence of chronic ulcer showed the characteristic male predominance, only 20 of the 142 patients admitted being women.

NATURE OF PROVOCATIVE FACTORS

Aspirin

In seeking the causes of the ulceration and its exacerbation which had led to haemorrhage, a strikingly large proportion of acute ulcers was first noted, and, as it is known that aspirin will lead to an acute haemorrhagic erosive gastritis (Muir and Cossar, 1955) in a number of those who take it, careful note was made of the patients' history of aspirin taking both past and recent and also of the type of preparation used. It was found that 205 of the ulcer cases (65%) had taken aspirin within 48 hours of the onset of haemorrhage while 109 had not. Of the 205 aspirin cases, 122 were classified as of acute and 83 as of chronic ulcers. It is, of course, evident that if aspirin causes an acute erosive gastritis it is unlikely that even the 83 cases were all or even largely bleeding from the chronic ulcer shown in the final radiograph and suggested by the previous history. It is known that chronic duodenal ulcers in particular react with an extreme erosive gastritis to aspirin (Muir and Cossar, 1955) while chronic gastric ulcers may be naturally associated with erosive gastritis. My colleague, Mr. Frank Forty (personal communication), very frequently finds haemorrhagic erosive gastritis as the cause of bleeding even where a chronic ulcer is present. This fact has to be remembered when planning the treatment of a bleeding ulcer. The possibility of multiple ulcers has also to be considered and in one of the non-aspirin cases at operation bleeding was found to be coming from a subacute gastric ulcer associated with a chronic duodenal ulcer, and in one aspirin case from an acute gastric ulcer with similar association. The proportion of patients bleeding from acute erosion after taking aspirin is, therefore, likely to be much higher than shown in Table I.

TABLE I.—TYPE AND AGE DISTRIBUTION OF BLEEDING ULCERS

Age (year)	Acute ulcer				Chronic duodenal ulcer				Chronic gastric ulcer			
	No operation		Operation		No operation		Operation		No operation		Operation	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Aspirin group:												
Less than 20	2	2										
21 to 30	2	2			5	1						
31 to 40	13	1	1		4	3	2					
41 to 50	12	7	[1] 3	1	3	1	3		2	1		
51 to 60	20	9	2		16	2	3		3			
61 to 70	10	10			12		4		3	2	2	
71 to 80	7	12			5				1	2	1	1
81 to 90	2	4								1		
Total	68	47	6	1	45	7	12		9	6	3	1
Nonaspirin group:												
Less than 20												
21 to 30	4	2			3							
31 to 40	2	2			4		1					
41 to 50	7	1			8	2	2	1	1		1	
51 to 60	8	3			7	1			4		[1] 1	
61 to 70	6	6			10	1			4		1	
71 to 80	4	4			4	1					1	
81 to 90		1					1					
Total	31	19			36	5	4	1	9		4	
Grand total	99	66	6	1	81	12	16	1	18	6	7	1

[1] 1 also had chronic duodenal ulcer.

This table also emphasizes the way in which aspirin ingestion appears to level up the incidence of ulceration as between the sexes, for the proportion of acute bleeding ulcers is actually much higher in women (67, with 48 aspirin takers out of 87 ulcer cases of all types) than in men (105, with 74 aspirin takers out of 227 ulcer cases). Men show the expected predominance in the chronic ulcers, 122 as against 20, with great predominance in duodenal ulcers, 97 (exclusive of one found not bleeding) as against 13 in women (Table I).

The figure of 65% for recent aspirin ingestion in my cases is higher than the 40% described by Alvarez and Summerskill (1958) and the one in eight after ingestion of aspirin for all ulcers cases (one in five for acute ulcers) mentioned by Muir and Cossar (1955). It does, however, accord with the figure of 70% given by Stubbe (1958) as the proportion of his patients losing blood after aspirin ingestion. The possible cause for the high proportion of gastric casualties after taking aspirin seen by the writer as well as the symptoms for which aspirin was taken in the various cases will be discussed later.

The gastritis caused by aspirin is largely a direct traumatic irritation of the surface of the stomach by the aspirin and was first described by Douthwaite (1938), by Hurst and Lintott (1939), and subsequently very ably by Muir and Cossar (1955 and 1959). In a widely haemorrhagic and oedematous gastric mucosa, particularly on the lesser curve, one or more small erosions are seen, and the duodenal mucosa may be similarly affected. Aspirin appears to act as an irritant most easily on an empty stomach (Lange, 1957; Muir and Cossar, 1959), and, by provoking a marked hyperacidity in stomachs where the mucous secretion is also subnormal, as in cases of chronic duodenal ulcer. It is apparently less irritant in enteric-coated capsules (Lange, 1957; Scott, Porter, Lewis, and Dixon, 1961) but apart from Schneider's findings (1957) it has not been generally found that soluble aspirin ('calcium aspirin') is less irritant than acid acetylsal, which is converted into that time-honoured substance for removing corns from the feet (acid salicyl) when acted on by hydrochloric acid in the stomach. This epidermolytic effect (Ivy, Grossman, and Bachrach, 1950) may at times be enhanced by the ability of salicylates to cause gastric ulceration and haemorrhage after subcutaneous or intravenous injection (Dodd, Minot, and Arena, 1937; Grossman, *et al.*, 1961) so a high blood salicylate level may augment the local irritative effect. The bleeding seen in 110 of my cases after small, often very small, doses of aspirin would, however, seem to emphasize the importance of its local gastric effect. I did not observe general signs of aspirin sensitivity in any of my cases (Honigsberger, 1943).

To examine the relative irritative effects of various aspirin preparations on the market the patients were asked carefully not only about the dosage but also the type of aspirin preparation taken. The comparative results are seen in Table IV. At this point it is perhaps not out of place to comment on the diversity of names for aspirin preparations, a reflection of the general multiplicity of titles for pharmaceutical products with which the whole problem of therapy is hagridden at the present day. Some of the names imply an aspirin content but this is not so with others, and patients have volunteered to me that they knew that aspirin did not suit them but did not realize that such tablets as Alka-Seltzer, Phensic, Antoin, Veganin, Hypon, or even compound codeine tablets contained it. In the past, as has been pointed out (Jennings, 1963), some aspirin-containing products, notably Alka-Seltzer, have been widely and intensively advertised as being of benefit for digestive complaints. As can be seen from Table II the soluble 'calcium aspirins' (Disprin, etc.) are as liable as the less soluble 'acid' aspirin products to promote haemorrhage. The two less widely advertised preparations, Macprin and Paynocil, which contain glycine (aminoacetic acid) to make them disintegrate and freely dispersible, appear but little in the list; indeed Paynocil was only taken by one bleeding patient (a cirrhotic) and in company with other aspirin preparations. No cases of bleeding from sodium salicylate administration were observed (cf. also Baragar and Duthie, 1960) but Scott and his co-workers (1961) found it liable to cause gastric bleeding when in tablet form, but did not test ordinary strengths of mist. sod. sal. (cf. also Grossman *et al.*, 1961).

In my series aspirin was taken as whole tablets, crushed tablets, and in suspension. As can be seen, many patients (110) bled after only a few tablets, *i.e.*, less than four (cf. also Stubbé, 1958), and in the remaining 95, some of whom took a mixture of a few tablets of one preparation with a few of another (*e.g.*, aspirin and Phensic or Anadin and Hypon), there were those who, while taking aspirin regularly, only took two or three tablets in the day for pain or at night for sleep. The

impression was strong that the tablets were most deleterious if taken on an empty stomach and particularly if so taken with some whisky or brandy in the time-honoured treatment for 'influenza'. In one case Disprin was taken with cortisone for rheumatism and this case is excluded. The other possible factors in promoting bleeding were often responsible for the symptoms for which the aspirin was taken (Tables III and VI), and these form an interlocking and interrelated complex which is a commentary on 'the way we live now'. Physical stress, tiring journeys, rushed meals, over-smoking, financial and business worries, poor sleep, and an increasing number of elderly people all were encountered frequently in the list. The part played by these influences in promoting gastric haemorrhage will now be considered individually, remembering all the while that headaches, muscle pains, and gastric discomforts, *i.e.*, symptoms for which aspirin is taken, are liable to be their resultant symptoms. For this reason the aspirin cases are listed separately from the others. The effects of other irritants, including alcohol and smoking, are considered but all the results probably show numbers less than the actual, for histories are inadequate in very ill patients and in those averse to admitting to nervous influences or overindulgence. The main results are summarized in Table III and, since nervous influences appear to be most frequent, they are considered first.

TABLE II.—NUMBERS OF CASES RELATED TO EACH TYPE OF ASPIRIN PREPARATION IN GASTRIC HEMORRHAGE

	Number of tablets taken				
	Acute ulcers		Chronic ulcers		
	Few [1]	Many [2]	Few [1]	Many [2]	Total
Free acid tablets: [3]					
Aspirin and genasprin	28	31	10	14	83
Aspro	8	3	3	4	18
Alka-Seltzer	9	1	10	8	28
Anadin	5	3	3	5	16
A.P.C.	2	2	1	1	6
Codeine compounds	4	10	3	3	20
Hypon		2	1	1	4
Phensic				2	2
Veganin	1	1	2	1	5
Beecham's powders	2				2
Soluble aspirin tablets:					
Disprin and codis	11	13	5	7	36
Antoin		1			1
Dispersible aspirin tablets: [4]					
Macprin	2				2
Paynocil	([5])	([5])	([5])	([5])	([5])
Total	72	67 (139)	38	46 (84)	223

[1] 4 tablets or less.
[2] More than 4 tablets.
[3] Aspirin compounded with calcium carbonate and citric acid.
[4] Aspirin with amino acid (glycine).
[5] Only once used by cirrhotic with 3 other aspirin preparations.

Nervous factors

Nervous factors operating in people predisposed by their personality will cause a peptic ulcer if together the degree of predisposition and the amount of imposed nervous strain sufficiently disturb the patient. Family stress, bereavement, and financial trouble were fairly frequent amongst my patients in imposing such strain, and as an instance may be quoted the gastric ulcer patient (not in the series) who had his first haematemesis in 1944 after his son had been killed and who did not bleed again till after the death of his wife many years later.

William Brinton (London, 1857) first stated that 'mental anxiety so frequently coincides with ulcer that we are fully entitled to regard it as a more or less immediate cause'. The type of personality of the ulcer patient varies but with Sullivan and McKell (1950) I have found that emotional conflicts resulting in anxiety, hostility, resentment, and insecurity often occurred amongst my patients. As a result (Minski and Desai, 1955) they were restless and showed unusual drive and attempts at achievement. A ward containing a number of convalescent, ambulant gastric patients seen at a distance may be remarkably reminiscent of a lion's cage!

This state of mind, which often requires sedation, is that which Alexander (1934) has stated to be responsible for chronic excitement of the stomach and it has since been shown (Wolf and Wolff, 1942, 1943) in their fistula subject, Tom, that anxiety and hostility cause hypersecretion, hypermotility, and hyperaemia of the gastric mucosa. Mittelmann, Wolff, and Scharf (1942) further showed that these and kindred destructive emotional reactions could reactivate peptic ulcers and cause recrudescence of symptoms. Davies and Wilson (1937 and 1939), in a controlled series of cases, found that emotional stress briefly preceded perforation or haematemesis in 84% of their cases. Melton (1940) found that the outbreak of war caused an increase in haematemesis and perforation, and while heavier work and increased smoking participated in this increase the predominant factor was marked nervous strain (Table III).

In my patients, without deep probing, tension, anxiety, and frustration were evident frequent associations of haematemesis; fear was active in a gas-holder attendant nervous of heights. It was often hard not to feel that the increased speed of modern life greatly accentuated these mental states, an impression which does not decrease with observations beyond the hospital walls.

TABLE III.—OTHER INFLUENCES THAN ASPIRIN IN GASTRIC HAEMORRHAGE

	Aspirin cases (205)		Nonaspirin cases (109)		Totals		
	Acute ulcers	Chronic ulcers	Acute ulcers	Chronic ulcers	Aspirin	Non-aspirin	Grand totals
Nervous strain:							
Male	32	32	16	16	64	(96)32	139
Female	22	2	13	6	24	(43)19	
Physical strain:							
Male	18	20	10	19	38	(67)29	79
Female	6	3	2	1	9	(12)3	
Smoking:							
Male	29	40	12	30	69	(111)42	120
Female	2	5	1	0	8	(9)1	
Alcohol: [1]							
Male	(5)20	(7)11	(5)9	(10)12	31	(52)21	57
Female	3	0	(1)2	0	3	(5)2	
Acute infections (mainly respiratory): [2]							
Male	17	15	2	2	32	(36)4	53
Female	13	2	2	0	15	(17)2	
Chronic infections (mainly respiratory):							
Male	4	12	2	6	16	(24)8	28
Female	2	1	0	1	3	(4)1	
Arteriosclerosis and hypertension:							
Male	16	9	7	8	25	(40)15	76
Female	23	6	6	1	29	(36)7	

[1] The figures in parentheses show the approximate number of heavy drinkers in each group.
[2] Inclusive of chronic infection in exacerbation (11 cases).

In all there were 139 cases, 96 men and 43 women, showing definite evidence of nervous strain, and amongst these were 42 patients who were troubled by business worries, 33 from the aspirin list and nine from the non-aspirin list. There were also 48 patients whose worries were concerned with family affairs (illness, death, loss of home) and 19 of these were from the aspirin list and 29 from those in the non-aspirin list. It is interesting, but perhaps not surprising, to find that the main number of aspirin takers was in the business group, with 28 men out of 33 equally divided as cases of acute and chronic ulcer. In the non-aspirin group (nine) of business worriers all were men and seven had chronic ulcers. In the large group (29) of those with domestic worries, bleeding without aspirin, there was a slight predominance of women (15), with nine acute ulcers and six chronic as against eight acute and six chronic ulcers in men in this group. In the group of 19 with domestic worries who bled after aspirin, 13 were men and six were women, and, not surprisingly, there were eight acute ulcers in men and five acute ulcers in women amongst these, for many domestic crises are acute matters.

In the 94 cases not classified in these groups the emotional states of anxiety, tension, or aggression were evident, but the history of precipitating trouble, if present, was not forthcoming; suppressed worry is of course particularly injurious to health (Avery Jones, 1957).

Physical strain

Seventy-nine patients were found in whom physical strain seemed to be the chief factor, or at least the presenting factor in precipitating haemorrhage. It is as difficult to separate the physical strain from the nervous tension which lies behind it as to classify the exact nature of a nervous strain where business and domestic issues have much interplay, as in two men who lost their jobs. Indeed four men with different types of ulcer suffered from the double strain of supporting seriously invalid wives (strokes, Cushing's syndrome) and carrying on with their work. Amongst the 79 patients rushed and often irregular meals were the most frequent finding and no doubt occurred more often than in the 49 who especially mentioned it; 27 of these came from the a-spirin group and 24 of them were men. Thirteen of these patients had acute ulcers, and 11 were chronic, 10 being duodenal and one a stomal ulcer. Of the three women in the aspirin group one had a chronic duodenal ulcer and two had acute ulcers. In the non-aspirin group of 22 'meal-scampers' all were men apart from one woman with a chronic duodenal ulcer. In the male group there were 13 chronic ulcers, 11 duodenal and two gastric ulcers; eight in this group had acute ulcers.

The almost equal division of the total of 49 who scamped their meals between acute and chronic ulcers appeared to be related to the fact that in many of the patients with acute ulcers the meal routine had been more recently upset by increased work; in the patients with chronic ulcers as a general rule the bad habit was longstanding and often associated with heavy smoking. The greater proportion of acute ulcers in the aspirin group is not surprising. Only rarely did heavy work alone, or strain due to heavy lifting, seem to precede the bleeding.

Dental sepsis was only noteworthy in eight patients, and one of these, a chronic alcoholic with a chronic gastric ulcer, had an alveolar abscess. Two other patients had had teeth extracted just before admission but without much loss of blood till they took aspirin for jaw pain. Eight of the 10 patients had taken aspirin and seven of them had chronic ulcers; only two were women.

One young woman bled from an acute erosion just after giving a pint of blood to the blood bank. Two other patients had operations before bleeding, one a thumb amputation and the other his third unsuccessful hernia operation; both had acute ulcers but both had taken aspirin. One patient with a fractured femur had a haematemesis associated with aspirin a week after his accident, but I saw none of the spontaneous, gross erosive mucosal lesions so graphically described by Breckenridge, Walton, and Walker (1959). It is impossible to leave physical factors without mentioning the burden of age (to be considered later); of illness (such as in three cases of hemiplegia); pain as in arthritis, of which there were many cases, including five of painful spinal arthritis; or of the loss of a leg (one case). Of these, the three with most severe spinal arthritis, the one with a leg amputation, and two hemiplegics had chronic ulcers.

Local irritative factors

This group comprises heavy smokers and those who directly insulted the gastric mucosa by swallowing irritative substances, notably alcohol, and is additional to the aspirin group already described. As can be seen from Table III the majority of patients in this group had also taken aspirin.

Smoking: Avery Jones (1957) has suggested that the increase in smoking may be directly related to the increased incidence of peptic ulcer. On the other hand Hojer-Pedersen (1958) follows the 'oral dependency' theory of Alexander (1934) in considering that the conflicts in the ulcer personality predetermine a tendency to smoke and drink too heavily.

In my list, oversmoking, with 120 patients admitted for gastric haemorrhage, closely rivals nervous factors in the same complaint. Seventy-seven of these patients had also taken aspirin recently and 43 had not. The predominance of men and of chronic ulcers in the two groups is evident from Table III, and of the 18 cases of men developing duodenal ulcer before the age of 40 years, 14 were heavy smokers and three of the others were alcoholics. Since the smoker may tend to underestimate his tobacco consumption, all those who confessed to 15 cigarettes daily or their equivalent in tobacco were placed in this group. As noted earlier many of them also had rushed and irregular meals. It should also be emphasized here that out of 37 men with business worries, 29 were heavy smokers, and 18 of these had chronic ulcers, usually duodenal, 11 patients coming from the aspirin group and seven from the non-aspirin bleeders. Two worried business women, who smoked very heavily, had ulcers, one acute, the other, less than 40 years of age, had a persistent duodenal ulcer.

Alcohol: In my experience drinking alcohol may help to predispose to ulceration or may rapidly precipitate gastric bleeding. Those who bled after alcohol were grouped as: (1) 'heavy drinkers, *i.e.*, consistently heavy drinkers and those liable to very heavy bouts of drinking; and (2) 'provocative' drinkers, *i.e.*, those who drank just beyond moderation, particularly at week-ends, or who took too stiff a 'curative' tot of spirits.

Of the group of heavy drinkers, there lay confessed 28; 12 had also taken aspirin before bleeding and 16 had not. (Cases of hepatic cirrhosis are not grouped with these cases.) All were men except one woman who developed an acute ulcer as a result of recently drowning her domestic trouble in drink. Eighteen of the men had chronic ulcers (11 duodenal, eight gastric, and one with both ulcers). The prominence of gastric ulcer in this group is attributable to the fact that this type of ulcer follows chronic gastritis.

There were 29 cases of less heavy or 'therapeutic' drinking; 22 of these were associated with taking aspirin. Of the non-aspirin group, one patient was a young man who took 17 pints of beer to steady himself for the arrival of his first child, and another was a young provincial forgetting his business worries at a London party who was admitted drunk and vomiting blood; both had acute ulcers. Only four of the 29 were women, all with acute ulcers, and of the 25 men 19 had acute ulcers. As with smoking and worry, it would appear that the longer and harder the noxious influence is applied the more it is likely to cause chronicity in an ulcer.

Although my heaviest smoker (50 cigarettes daily) was also a heavy drinker, it is probable that not all the heavy drinkers were as ready to admit their smoking habits—or vice versa; but in all the alcohol takers there were 20 who admitted to heavy smoking and of these 11 also had business or domestic worry, eight coming from the aspirin group. A very small glass of wine taken at the end of a fast provoked bleeding in a Hebrew patient with a chronic duodenal ulcer.

Other irritants: These include all other preparations which might have assisted gastric haemorrhage, either alone or in conjunction with other factors. None of the patients complained of recent ingestion of irritative solid food.

Phenylbutazone was taken just before haemorrhage in three ulcer cases seen in this series, and in one seen shortly afterwards. In one it was taken in conjunction with aspirin, in two alone, and in one with spirits. In all but the case outside the series, with severe spinal arthritis, the ulcers were acute. The action of phenylbutazone on the stomach is considered to be both local and systemic by Kirsner and Ford (1955), who found that it increased gastric acid flow, particularly in duodenal subjects.

Magnesium sulphate, as laxative 'salts' was taken, for 'rheumatism' in five cases: twice with aspirin, once with gin, once with tetracycline, and once alone. All these patients had acute ulcers except the last named and he had a large chronic gastric ulcer which required operation.

Only two patients had had anticoagulants (Dindevan): one with acute ulcer had been given Dindevan for femoral embolism from a severe mitral stenosis, and one with a large gastric ulcer causing chest pain was wrongly suspected of coronary thrombosis; he required operation.

Two patients received cortisone before bleeding; one with a short course also had aspirin, and quickly recovered from an acute erosion; the other after long treatment for rheumatoid arthritis died of a chronic gastric ulcer and a ruptured necrotic jejunum. In two further non-aspirin cases bleeding from acute erosions was preceded in one by sulphonamide therapy for tonsillitis and in the other by the use of an antihistamine preparation for giant urticaria.

Infective factors

My cases of infection (most were of respiratory type) were grouped into (a) acute or acute exacerbations of chronic and (b) chronic infection. Of the 70 cases in this group, 42 were acute, 11 were acute exacerbations of chronic infection, and 17 were of chronic infection only (Table III). A dental abscess and a neck carbuncle were included amongst the acute infections but all the others were respiratory and largely of the influenzal or severe coryzal type. Of the 53 patients in group (a), 39 bleedings were preceded by this type of infection and of these four developed pneumonia. In the chronic group of infections were two men with extensive dental sepsis and chronic duodenal ulcers and one of these developed suppurative pneumonia after his haematemesis. He responded well to antibiotics, which were used in these cases whenever infected sputum or appreciable fever occurred. Otherwise the chronic infections were entirely chronic bronchitis with

three cases of bronchiectasis. From Table III of the predominence of aspirin-takers in this group (55 of the total) is apparent and supports Kelly's (1956) suggestion that taking aspirin for influenza is a frequent cause of gastric bleeding; 36 patients with acute ulcers in the aspirin-infection group is in accord with the expected effects of aspirin. Of these 36, the majority had acute infections for which several, presumably feeling that fever, like sorrow, may yield to alcohol, had also taken a stiff dose of spirits.

It has long been recognized that virus infections may cause gastritis or may exacerbate pre-existing peptic ulcer symptoms (Emery and Monroe, 1935). Also that in chronic repiratory disease the additional elements of hypoxaemia and a tendency to visceral congestion from right heart decompensation both have adverse effects on the gastric mucosa (Avery Jones, 1957; Allibone and Flint, 1958; Flint and Warrack, 1958).

The association of chronic gastric and duodenal ulcers with chronic bronchitis and emphysema has been often remarked (Weber and Gregg, 1955; Latts, Cummins, and Zieve, 1956; Avery Jones, 1957). The proportion of chronic ulcers seen amongst my chronic infection cases is emphasized in Table III though, exceptionally, one of the three bronchiectatics died of right heart failure and a widespread haemorrhagic gastritis and duodenitis, probably because he had recently taken aspirin. Terminal haemorrhage from acute ulcers did however feature prominently in the cases of emphysema and chronic cor pulmonale of Flint and Warrack (1958), often in association with recent respiratory infection.

Arteriosclerosis and hypertension

Most of the patients in this group were over 65 years of age but only those with marked vascular change were included, so the figures (Table III) are probably an understatement. One man of 39 years with very high blood pressure had an acute erosion after taking aspirin for headache, and of the other 75 patients 53 had taken aspirin for the aches and pains of old age. As has been mentioned, physical disability and the need to fend for oneself were prominent features of this group; the increased proportion of women in it (nearly one half) is noteworthy but not surprising.

Baker (1947) found hypertension in 5% of a series of 542 cases of bleeding ulcers mostly associated with mucosal lesions, in which he felt that the hypertension facilitated bleeding. Both Goldman (1936) and Kruse (1937) thought that arteriosclerosis was an important factor in causing heavy haemorrhage from peptic ulcers and in increasing the mortality rate.

Other cardiovascular considerations

In one group of this series chronic cor pulmonale has been mentioned and in another fibrotic myocardial change resulting from coronary arteriosclerosis has been implied. Apart from these two groups little heart disease was encountered during the observations. There was one patient with an appreciable ventricular septal defect and a chronic ulcer; four were cases of chronic rheumatic heart, all with marked mitral disease and one with aortic reflux, and all with acute ulcers. There were also four cases of coronary thrombosis. One of these was terminal in an old man after a very heavy haemorrhage; the other three occurred respectively two years before, one year before, and one year after the gastric haemorrhage.

This dissociation between peptic ulcer and coronary thrombosis is also striking in the very large numbers of coronary thrombotic patients admitted to my wards; very few indeed have a gastric history to preclude the use of anticoagulants. Since stress is blamed for both disorders it is curious to find that it strikes above the belt in one group and below it in the other, but rarely in both places. Leaving aside all psychological consideration of repressed oral desires causing overstimulation of the gastrointestinal tract (Rosenbaum, 1954) I have been impressed with the marked physical overactivity and lack of obesity in my peptic ulcer patients and these two facts surely lessen the tendency to coronary thrombosis.

Other observers have found a varied linkage between peptic ulcer and coronary thrombosis. Walsh, Bland, Taquini, and White (1941) in 2,737 necropsies found no significant association between peptic ulcer and coronary disease. Morrison and Gonzalez (1952) felt that nervous (vagal) causes might lead to the two conditions in the same patient but also felt that the high lipoid content of many gastric diets might predispose to coronary disease, a possibility which was also stressed by Briggs, Rubenberg, O'Neal, Thomas, and Hartroft (1960). The liability of coronary thrombosis to occur in the elderly after severe ulcer haemorrhage, observed in my series, has also been noted by Crenshaw (1962).

Occupational factors

In their survey of the influence of occupation in the aetiology of peptic ulcer, Doll, Avery Jones, and Buckatzsch (1951) list the view of other investigators in this field, and the results are varied, probably to some extent as a result of the diversity of districts under review, though this does not entirely explain why doctors in Britain, found by Alsted (1942) and Doll *et al.* (1951) to have a high incidence of peptic ulcer, in Sweden (Ihre and Muller, 1943) showed a low incidence. Doll *et al.* (1951) also found responsible work (foremen and business executives) to bring a high incidence of ulcer and agricultural work to cause a low incidence (cf. also Alsted (1942)). The nature and position of my work brought no doctors or agricultural workers into the series, but many professional, responsible and skilled workers, and the high incidence of chronic duodenal ulcer in these, often heavy-smoking men, can be seen from Table IV. 38 such sufferers still being fully active whilst a number of the 24 retired had in their time been similarly employed. Doll *et al.* (1951) also did not find evidence of bus drivers being predisposed by their work to ulcer and there was only one such, with an acute ulcer, in my series. Five patients in all, who did not take aspirin, drove large vehicles and three of these had acute ulcers. In the aspirin cases the train driver had an acute ulcer and the two long-distance lorry drivers had chronic duodenal ulcers. One of these improved with new work, but the figures are not impressive, hardly a surprising fact when a large proportion of my patients were car drivers, often under trying conditions.

With Doll *et al.* (1951) I did not find shift work markedly detrimental to the stomach, only two of my patients blaming this mode of working.

TABLE IV.—OCCUPATIONAL CATEGORIES OF ULCER PATIENTS

	Professional, responsible, skilled, self-employed			Semi-skilled and subordinate posts			Unskilled			Household duties [1]			Retired		
	Acute	Chronic duo-denal ulcer	Chronic gastric ulcer	Acute	Chronic duo-denal ulcer	Chronic gastric ulcer	Acute	Chronic duo-denal ulcer	Chronic gastric ulcer	Acute	Chronic duo-denal ulcer	Chronic gastric ulcer	Acute	Chronic duo-denal ulcer	Chronic gastric ulcer
Aspirin cases (205):															
Men (143)	35	22	1	13	12	5	10	8	3				16	15	3
Women (62)	2			2	1		9			23	6	3	12		4
Non-aspirin cases (109):															
Men (84)	6	16	2	13	7	4	7	8	2				5	9	5
Women (25)				2	1		2	2		10	2		5	1	
Totals	43	38	3	30	21	9	28	18	5	33	8	3	38	25	12

[1] 6 housewives from aspirin group and 2 from nonaspirin group with other work are placed in semi-skilled and unskilled categories.

Intrinsic factors

If we exclude the personality of the patients the main intrinsic factors to be considered are those of sex, age, family history, and blood group.

Sex: There is a great preponderance of men amongst cases of chronic ulcers (122 : 20) with a particular male predisposition in duodenal ulcers (97 : 13) and a smaller predisposition in chronic gastric ulcers (25 : 7). Two male stomal ulcers, classified as gastric, occurred in former sufferers from duodenal ulcer. Hanley (1964) correlates this male prevalence in ulcer formation with the greater secretory mass of peptic cells found in men.

In acute ulcers there is, in my series, a great levelling up between the sexes (105 men to 67 women), and particularly in the aspirin group (74 men to 48 women.) In these cases the effect of local gastric trauma is paramount and other considerations of less import, but it is noteworthy that women subject to major strains in the competitive world of business and industry tend to develop chronic ulcers, and the factor of sex, as compared with the environmental effects, dwindles in importance.

Age: Up to a point it may be said that the older we get the greater are our chances of peptic ulcer. Cates (1959) found that in men gastric bleeding showed an appreciable increase in the fourth decade; was high in the fifth, sixth, and seventh decades, and fell off in the eighth decade; in women the increase was gradual from the fourth to the eighth decade. As can be seen from Table I my figures concur with these findings in all classes of ulcer except in the female chronic list which is too small to be significant. The age of decrease in the incidence of ulcer or haematemesis coincides with the age of decreasing numbers at risk.

Family history: A clear family history of one or more near relations with peptic ulcer was found in 34 cases, 24 from the aspirin list and 10 others. Of these, 21 (13 men and eight women) had acute ulcers though one man had previously had a duodenal ulcer. Apart from this man there were 13 chronic cases (11 men and two women) and one of these, a man of 21 years, with a chronic duodenal ulcer, had three close relatives affected. Whether on the total reckoning or on that of chronic ulcers alone, 10% had a positive family history. The precise significance of this figure has to be viewed with environmental factors also in mind: the influence of nervous relations, family difficulties, heavy smokers in the family, and so on. One nervous woman with haematemesis confided that all her family were nervous and that her nephew developed his ulcer on D day. Many of those with a family history of ulcers were tense and anxious, and 13 were heavy smokers; the young man with the strongest family history was both. Further, since families often lean to the same occupation the family tendency to ulcer may, in part, at least, be determined by the environment at work. The family job and the family habits as well as the family personality may well be expected to predispose to family ulcers.

Although my figures, from which seven cases (four chronic and three acute) have been excluded because of incomplete evidence, do not greatly support the strength of inheritance of the ulcer tendency, Doll and Kellock (1951) did find that their two groups of cases of duodenal and gastric ulcer each had an independent hereditary factor. Despite this, Cleave (1962) is convinced that environmental factors are of far greater importance, a view supported by the persistently rising ulcer rate.

Blood groups

The hereditary factor in chronic peptic ulcer noted by Doll and Kellock (1951) can now be related to the observations of Roberts (1957) that duodenal ulcer is associated particularly with blood group O and that so to a lesser extent is gastric ulcer. Another feature of some hereditary significance is the associated finding of salivary ABO nonsecretion in duodenal ulcer (Clarke, Edwards, Haddock, Howel-Evans, McConnell, and Sheppard, 1956). In gastric ulcer patients Buckwalter and Van Scoy (1961) have found an increased frequency of blood group O in gastric ulcer patients and to a lesser extent in their siblings. In gastric carcinoma they follow other writers (Roberts, 1957; Race and Sanger, 1958) in relating the disease to blood group A and to a lesser extent they found the same group in the siblings of these patients.

In 40 of my cases, taken at random, there were 21 from group O, 14 from group A, three from group B, and two from group AB. No significant results can be deduced from such small numbers but seven of the patients with chronic duodenal ulcers were in group O, two in group A, and one in group B. The group O cases included no chronic gastric ulcer but the one case of gastric carcinoma tested was in group A.

Seasonal influence

Avery Jones (1957) found most admissions for bleeding from ulcers in the months of December, January, and February and least in June and July. Kelly (1956) found an increase of bleeding in the spring and autumn which he felt might be ascribed to the aspirin treatment of virus infections during those seasons. My figures (Table V) show the expected drop in June and July, but surprisingly high figures for August. There was no clear reason for this last, but it may be related to attempts to cover holiday absentees or even to the added stresses which affluence and the motor car now introduce into the holiday season.

The expected high figures in the first three months of the year certainly bear relationship to the virus infections prevalent at that time of year and to their popular treatment with aspirin. Also the greater strain of work at that time of year appeared to influence some cases.

Other conditions causing bleeding

During the four years there were 24 admissions for bleeding in addition to the 314 admissions for bleeding from peptic ulcer. In the aspirin group there were 16 admissions: five patients with hiatus hernia; six with hepatic cirrhosis; three with gastric carcinoma; one women with a gastric leiomyoma; and one young man with haemophilia. There was only one man with hiatus hernia in this group and one woman with cirrhosis, but the cases of gastric carcinomata were all in men. One of these was successfully treated by operation as was one hiatus hernia and the leiomyoma.

TABLE V.—SEASONAL INCIDENCE

	Month											
	January	February	March	April	May	June	July	August	September	October	November	December
Aspirin (acute ulcers)	13 (6)	10 (3)	8 (1)	6 (4)	8 (2)	4 (1)	10 (4)	13 (5)	10 (4)	16 (9)	13 (5)	11 (4)
Aspirin (chronic ulcers)	7 (2)	11 (3)	9 (2)	8 (1)	5 (0)	3 (1)	4 (0)	8 (1)	4 (2)	7 (1)	10 (0)	7 (1)
Total	20 (8)	21 (6)	17 (3)	14 (5)	13 (2)	7 (2)	14 (4)	21 (6)	14 (6)	23 (10)	23 (5)	18 (5)
Nonaspirin (acute)	4 (2)	7 (3)	4 (1)	2 (1)	8 (4)	3 (0)	4 (2)	5 (3)	2 (0)	7 (3)	3 (0)	1 (0)
Nonaspirin (chronic)	9 (1)	1 (0)	7 (1)	2 (0)	5 (1)	4 (0)	4 (0)	9 (1)	4 (0)	7 (2)	5 (0)	2 (0)
Total	13 (3)	8 (3)	11 (2)	4 (1)	13 (5)	7 (0)	8 (2)	14 (4)	6 (0)	14 (5)	8 (0)	3 (0)
Grand total	33 (11)	29 (9)	28 (5)	18 (6)	26 (7)	14 (2)	22 (6)	35 (10)	20 (6)	37 (15)	31 (5)	21 (5)

Total figures and (in parentheses) number of female cases.

The non-aspirin group of eight were all men. There were three cases of hiatus hernia, one having an acute peptic ulcer at the lower end of a short oesophagus. There were also three cases of gastric carcinoma and two of hepatic cirrhosis. One of the patients with carcinoma had a successful operation; the other two died. It should be emphasized that all the patients with hiatus hernia may well have also had acute peptic ulcers for, as Davidson (1958) has remarked, the ulcers in these cases, often occurring at the anterior margin of the gastric narrowing, are difficult to see in radiographs. One of my cases of this type bled 10 days after taking a moderate dose of aspirin. This patient was not counted in with the ulcer cases, but all who had no more than a small gastric protrusion above the diaphragm were so reckoned.

SYMPTOMS TREATED BY ASPIRIN

The predominant symptoms for which aspirin was taken are shown in Table VI in which the inducements to aspirin are arranged in order of frequency. A few patients had two equal symptoms *e.g.*, headache and arthritis, dyspepsia and insomnia, and a few took aspirin with little reason, but most had one chief symptom for relief. In the greatest number (66) this symptom was gastric discomfort: nervous dyspepsia, flatulence, or the more severe pains of chronic duodenal ulcer. One of this group, suffering from severe pain penetrating into his back, read in the daily press of the pain-killing properties of codeine and, not realizing that such tablets contained aspirin, bought a large bottle of them and for each pain went to the bottle and turned a number of tablets into his palm and swallowed them with a little water. The power of television and the press and the confusing nomenclature of aspirin-containing tablets must be blamed for the type of severe haemorrhage which ensued in this case and required operation. It is most unfortunate that aspirin has come to be taken so frequently for the very group of complaints where it is likely to be most hurtful. For such complaints as influenza (often together with the added menace of spirits), 'rheumatism', arthritis, and headache, aspirin is of course a time-honoured remedy and is taken deliberately but without knowledge of its possibile ill consequences. In many such cases it is naturally taken on an empty stomach when its ill effect is likely to be most serious.

TABLE VI.—PRINCIPAL CAUSES LEADING TO TAKING ASPIRIN

Principal cause	Number of cases
Stomach pains (from both organic and functional dyspepsia)	66
Infections (mainly acute respiratory)	42
Headaches	40
Limb pains (osteoarthritic, muscular, sciatic, etc.)	26
Mental symptoms (worry, tension, etc.)	18
Insomnia (often in old age)	13
Backache (osteoarthritis etc.)	10
Toothache	8
Anorexia (or as tonic or prophylactic)	3
Colic	1
Post-operative (thumb)	1
Total	228

TREATMENT AND OUTCOME

It is not the purpose of this paper to deal in detail with treatment. The patients described bled in amounts from a few ounces to heavy and recurrent bleeds associated with severe shock. Rest, with adequate blood transfusion and anti-shock measures where required, were the main elements of treatment. Where necessary, sedatives were used to secure rest and the patients were given increasing gastric diets after initial short periods on largely fluid or soft food; alkalis and anticholinergic drugs were given in the usual manner, as were iron and ascorbic acid. In dealing with such a large number of aspirin-preceded haemorrhages and therefore, with many presumed acute lesions, I attempted wherever possible to avoid operative interference (c.f. Gilmour, 1961). The patients who had bled with moderate severity were, therefore, given an initial transfusion of 2 or, at the most, 3 pints of blood (1 to 1.5 litres) in the belief that overloading of the circulation with large volumes of blood was likely to restart a subsiding haemorrhage. In a case where the history strongly suggested acute erosion this type of transfusion was

repeated, if renewed bleeding became evident, but a still further bleed was taken as an indication for surgery. Only seven such cases came to operation, one woman and six men from the aspirin group, and one of the men had a chronic duodenal ulcer as well as acute ulceration. These seven are evidence that it is not always possible by conservative measures to arrest the severe bleeding which may occur in acute erosive haemorrhagic gastritis. But they are a very small minority and it is notable that all followed ingestion of aspirin.

In those with a history suggestive of chronic ulceration, operation was done for the second appreciable bleeding and in this group were 25 cases, 16 after aspirin and nine not so treated. There were eight gastric ulcers (four in each group) and 17 duodenal ulcers, 12 after aspirin; 16 of the duodenal ulcers were in men. Of the chronic gastric ulcer group only one (in the aspirin list) was a woman, and one man in the other list had a subacute gastric ulcer associated with a chronic duodenal ulcer. Avery Jones has found the need for operation greater in old patients, and though the ages were widely distributed in my cases (Table I), nine of them were over 65 years.

All the seven acute ulcer cases needed emergency operation, as amongst chronic ulcers did 10 of the aspirin group and five of the non-aspirin group. In the others a slightly delayed operation was performed when the patients were in optimal condition; these cases had nearly all had earlier haemorrhages. Other cases of chronic ulcer on the lists were treated by still later operation, but are not considered here.

COMMENT

Three hundred and thirty-eight patients admitted for upper alimentary bleeding were seen in four years in one general medical unit, and these were only part of the hospital admissions for this cause. Even those who dispute the existence of an 'ulcer personality' could not, from my evidence, overlook a large group of tense, conscientious, self-driving and even aggressive people in such admissions. With modern conditions of business routine, and to a less extent of domestic life, as competitive as they are, these people pressing into the front of the battle are likely casualties. Misfortune, fear, fatigue, fuss, frustration, frenzy, and even folly and infection, are all hostile influences. Self-inflicted and environmental effects were a detrimental combination in many of my patients, leading to acute or chronic ulceration.

Pulvertaft (1959) has shown the effect of urbanization in leading to increase in ulcer incidence, and the consequences of urbanization, bad mental habits, *e.g.*, anxiety, bad physical routine (fatigue, rushed meals, oversmoking), and bad medication lead on through gastric disorders and ulcers to gastric bleeding.

We have now passed from the 'aspirin age' into the 'tablet age' but still far too much aspirin is taken without due thought or as a result of unscrupulous advertisement. Why it causes bleeding in some and not in others has been implied by my findings. There is more than presumptive evidence that the group of people just considered were most likely to have gastric mucosal congestion (Wolf and Wolff, 1942, 1943; Mittelmann, Wolff, and Scharf, 1942) whether they had an ulcer or not, and unfortunately under present conditions this kind of group is most prone to take aspirin. Aspirin is thus one large factor amongst the many which add together to produce a haemorrhagic ulcer. If it causes bleeding before chronic ulceration has occurred then an improved régime may avert persistent trouble, but where the warning is not heeded chronic ulceration has been found to follow. It is suggested that the failure of ulcers to heal is due to strong and continued action on the gastric mucosa of such noxious influences as have been described. The action of aspirin is certainly local and irritative; it is also suggested that it may either have a lesser effect from the hypothalamus via the vagi or through the gastric blood supply.

After aspirin, even acute ulcerations, which can be widespread, may necessitate surgical treatment but my findings suggest that the need for immediate surgical treatment of bleeding ulcers has been greatly diminished in recent years by the greater use of judicious blood transfusion (Kekwick, Maycock, Marriott, and Whitby, 1941).

Of the 24 assorted cases of bleeding (16 after aspirin) seven came to operation, including four patients with gastric carcinoma, one developing in a chronic simple gastric ulcer. The other three cases were of leiomyoma, hepatic cirrhosis, and hiatus hernia.

Of the admissions for ulcer, seven out of 172 patients with acute ulcers (4%) and 25 out of 142 with chronic ulcers (17.6%) came to operation immediately or

soon after bleeding. Of these, three ulcers were also on the point of perforation, four were penetrating, and one duodenal ulcer was stenosed. There was an operative mortality of five (15.6%), one in a case of acute ulcer and four in chronic ulcers. The patient with acute ulcer had toxic myocarditis from influenza; one of the patients with chronic ulcer who died was a chronic alcoholic; one had severe chronic bronchitis and asthma; the other two were respectively 75 and 82 years of age.

Cates (1959) has pointed out that haematemesis patients do not often die as a direct result of a bleeding ulcer but from associated conditions. This was as true of my non-operative deaths as of those just mentioned, as can be seen from Table VII. There were in all 14 ulcer deaths in this group out of 314 admissions (less than 4.5%).

Some patients were temperamentally or socially unable to control their ulcers by dietary care and moderation in alcohol and tobacco; they later required operation. The others who did not come to operation have been followed in large numbers and as a result of improved régimes most have maintained satisfactory health, though a few have needed operation. Those who have kept well have benefited from the dramatic warning given by the bleeding to mend their ways, a result not unlike the result of the heeded warning of a haemoptysis in pulmonary tuberculosis.

In my lists were three patients who had had a previous gastroenterostomy and eight with partial gastrectomy. Two of the gastroenterostomy cases had stomal ulcers, but all the other cases had acute lesions, though one chronic alcoholic who had had partial gastrectomy for duodenal ulcer later developed a chronic gastric ulcer. Two other cases, a man and a woman, first seen with acute ulcers, developed gastric craters after prolonged domestic trouble, the woman, after bereavement, showing both gastric and duodenal ulcers.

In general I have found gastric ulcers more responsive to medical treatment than are duodenal ulcers.

TABLE VII.—CAUSES OF DEATH IN ALL CASES OF BLEEDING

Aspirin cases				Nonaspirin cases			
Cause of bleeding	Associated conditions	Sex	Age	Cause of bleeding	Associated conditions	Sex	Age
Acute gastric ulcer	Coronary atheroma, myocardial fibrosis, bronchopneumonia.	Male	79	Acute gastric ulcer	Chronic ischaemic heart, myocardial failure.	Male	66
Do	Bronchopneumonia, chronic ischaemic heart, osteoarthritis.	Female	83	Acute duodenal ulcer (large)	Atheroma (marked), chronic ischaemic heart.	Female	90
Acute duodenal ulcer	Pulmonary embolism, osteoarthritis.	Male	76				
Acute gastric ulcer	Bronchiectasis, right heart failure	do	49	Acute duodenal ulcer	Mental depression	do	62
Do	Cerebral thrombosis, chronic bronchitis.	Female	84	Chronic gastric ulcer (steroids)	Rheumatoid arthritis, ruptured jejunum.	Male	56
Do [1]	Influenzal myocarditis	Male	55				
Chronic duodenal ulcer	Influenzal pneumonia	do	68	Chronic gastric ulcer (very large).	Pulmonectomy (2 yr previously)	do	61
Do	Myecardial infarct	do	78				
Do	Bronchiectasis and emphysema, right heart failure.	do	77	Chronic duodenal ulcer (large posterior). [1]	Chronic ischaemic heart	do	82
Do [1]	Chronic bronchitis and emphysema, bronchospasm.	do	67	Chronic duodenal ulcer [1]	Marked arteriosclerosis, large left ventricle.	do	77
Do [1]	Chronic alcoholic	do	59				
Chronic gastric ulcer [1]	Chronic ischaemic heart	do	75				
Gastric carcinoma [1]	do	do	75	Gastric carcinoma [1]		do	52
Hepatic cirrhosis	Chronic alcoholism	do	48	do	Chronic ischaemic heart	do	77
Do		do	58	Hepatic cirrhosis	Bronchiectasis	do	62
Do		Female	78				

[1] Postoperative deaths.

SUMMARY

The cause for bleeding from the upper alimentary tract has been considered in 321 cases from a suburban area in 338 consecutive admissions for this symptom. The expected predominance of men was found amongst the admissions for ulcer, 227 men and 87 women, but the number of patients bleeding from acute gastric erosion after aspirin (205) has increased the proportion of women in the series. It is suggested that aspirin causes an acute erosive gastritis mainly by local action and that this may also be the cause of bleeding even when a chronic ulcer is present. For this reason an attempt was made to defer operation in all patients bleeding after aspirin and in the series only 22 of the 314 patients with bleeding ulcers needed emergency operations. Only one patient, a woman of 62 suffering from marked mental depression, died merely as a result of heavy bleeding without having an operation. The other 18 patients who died due to ulcer, whether post-operative or otherwise, all had serious physical disability.

That aspirin causes bleeding in some and not in others appears to be due to the fact some have an increased acid-pepsin secretion in their stomachs. The association of this state with family inheritance, the blood group, and the ABH salivary secretion is mentioned, but the series particularly seemed to emphasize the importance of extrinsic factors: excessive emotion, fatigue, anxiety, infection, alcohol, irregular meals, and heavy smoking. It is concluded that these factors, which can increase gastric acidity or cause gastritis, can also thereby facilitate the erosive effect of aspirin. 'The gun must be loaded in order for an explosion to occur when salicylates pull the trigger' (Grossman *et al.*, 1961). And my cases also suggest that when a number of the malign influences just mentioned are conjoined then an intensification of one or more may precipitate the haemorrhagic explosion without the triggering influences of salicylates. They further suggest that these influences, becoming more frequent and intense in present-day urban life, are the causes of the observed increase in the number of peptic ulcers. This type of life does tend to lead to taking aspirin, so caution against its indiscriminate use and advertisement is enjoined.

In the series a divergence is also noted between the incidence of peptic ulcer and another increasingly common complaint often attributed to stress, coronary thrombosis.

That hereditary did not play a large causative part in the series may be attributed partly to the strength of operative extrinsic influences and partly to the large proportion of acute ulcers. In a one-man survey the results must necessarily be part impressionistic but I have tried to leave a large assembly of facts to speak for itself.

I am indebted to my colleague, Dr. Eric Topham for the very considerable help he has given me in the radiographic investigation of my cases.

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Mr. GOLDHAMMER. No. 3, the objection was made by Miles Laboratories that the toxicity of aspirin was not applicable to Alka-Seltzer because Alka-Seltzer is a strongly buffered solution. If it is applicable to anything it would be applicable to the tablets, to dry materials taken internally, perhaps in heavier concentration. I don't know what the rationale is.

This was rejected by the panel. I don't know whether it was proposed, but in the final order of the committee the committee amplified its statement, as you indicated, Mr. Hutt——

Mr. HUTT. Yes.

Mr. GOLDHAMMER. And this time touched upon the toxicity of aspirin/antacid solutions, in other words, talked about the toxicity of strongly buffered aspirin solutions.

It states——

Mr. HUTT. Which, I might add, points out that there was no improper influence whatever.

Mr. GOLDHAMMER. However, in the final order, it disposes of it all, because the final order says, "It is safe"——

Mr. HUTT. No.

Mr. GOLDHAMMER. Let me finish, please—"specifically when taken as a solution." I will be happy to read the final order to you.

Mr. HUTT. Would you compare it, please, with the proposed regulation, Mr. Goldhammer? The proposal says the identical thing.

Mr. GOLDHAMMER. That is correct. The proposal came after Miles Laboratories' request.

Mr. HUTT. Let me go back. The language that you are talking about with regard to the lack of safety, potential toxicity, is in the very document which contains the panel's recommended language for the regulation which states the product is safe.

Is that correct?

Mr. GOLDHAMMER. That is correct.

Mr. HUTT. That was not changed at all.

Mr. GOLDHAMMER. In the order that FDA adopted——

Mr. HUTT. That is the same thing.

Mr. GOLDHAMMER. Is that the order suggested by the panel or is that something which FDA draws up based upon the report?

Mr. HUTT. That was the proposed regulation. The recommended regulatory language was adopted by the panel as part of its recommendation. This was not done by FDA independently. What the panel did was to conclude that this language, on page 8724, saying that an antacid may contain any generally recognized, et cetera, ingredient, is intended to reflect their conclusions from this entire report. That was not changed, and it was not changed by the Commissioner.

I must confess I am having difficulty understanding your argument because there was no change made.

Mr. GOLDHAMMER. I do not say it was changed. I am just saying that what Miles Laboratories wanted, namely, its use as a solution, as an antacid and an analgesic concurrently, is fundamentally what ultimately was adopted by the Food and Drug Administration in its order.

Mr. HUTT. No; that is literally not true. They disagreed with what FDA did.

Mr. FOUNTAIN. You can reconcile that later. You can get together to see whether you can come to a meeting of the minds.

At least I am in a state of indecision about it. I have just a few more questions before I will have to leave.

There is one final point that I think requires clarification and that is the effect of category III classifications.

The panel of experts apparently has had difficulty in distinguishing between category II and category III. Is that right?

Mr. HUTT. I do not think they have had a tremendous difficulty, Mr. Chairman. In a few isolated instances they have.

Mr. FOUNTAIN. I must confess my own uncertainty as to the two classifications. I would like you to explain the difference.

Mr. HUTT. Surely. It involves, obviously, a judgment of experts as to whether an ingredient is either hazardous or potentially hazardous or for which, even if there is no hazard, there is no sound medical rationale for its possible effectiveness; or for which there is clear evidence that it is ineffective; which would put it into category II.

In those situations it goes into category II.

Where there is no potential health hazard, where there is possibly a sound medical rationale or the availability of good testing methods that would produce information to demonstrate safety or effectiveness, whichever one is in question, then the panel will put it in category III.

There is a built-in safeguard in category III, and that is that the testing must begin within a specified period of time or the ingredient must be deleted. Category III does not give anyone an automatic extension. It gives them a very short period of time within which to decide whether to pursue the matter through continued testing.

Mr. FOUNTAIN. I just find it difficult to comprehend how you can have partial general recognition of safety and efficacy. Either the product, it seems to me, is generally recognized as safe and effective

by the qualified experts, or it is not. Bearing in mind the court's interpretations of the expression "generally recognized as safe," certainly the Food and Drug Administration does not suggest a third category, namely, partially generally recognized as safe and effective; does it?

Mr. HUTT. No, sir. What we are doing is what the courts have recognized, to allow a transitional period which will permit us in a uniform and comprehensible way to interpret and apply the law.

Mr. FOUNTAIN. It speaks only in terms of generally recognized safety and effectiveness. The implication is that if it is generally recognized as safe and effective it is not a new drug and does not require premarket clearance.

Mr. HUTT. Again, there is a concept of transition built into the regulations which, as I mentioned, the courts have permitted us and specifically authorized us for OTC drugs to engage in. A category III condition is in an uncertain status until it is resolved one way or the other. One can neither say that they are or are not generally recognized as safe at that particular moment in time.

Mr. FOUNTAIN. One more bit of discussion about category III as it relates to the only monograph which has been finalized; namely, the antacid monograph published in the June 4, 1974, Federal Register.

The only allowable claims for antacid/analgesic combinations such as Alka-Seltzer in the monograph are detailed, as I understand it, in sections 331.15(b) and 331.30.

The allowable indications for uses are limited to use solely for the concurrent symptoms requiring an analgesic and an antacid to alleviate the following symptoms only: "heartburn, sour stomach, and/or acid indigestion." Is that correct?

Mr. HUTT. Those are the only category I claims, yes.

Mr. FOUNTAIN. Is the monograph now fully effective?

Mr. HUTT. I believe there are one or two remaining issues. The answer is "No." There is a question of a test method and one other question, I believe, which is outstanding at this moment.

Mr. FOUNTAIN. The monograph at the present time does not have the full force and effect of law?

Mr. HUTT. No. It is very close. Particularly the test method, and another question concerning a general warning which was not promulgated until fairly recently, have delayed the effective date. We will probably have to require an extension of time to meet that general warning.

In general terms I think you will find that virtually all antacids today are in compliance.

Mr. FOUNTAIN. Is it fully effective as to therapeutic claims?

Mr. YINGLING. Yes, except for the——

Mr. HUTT. I think the answer is "Yes." Could we please submit that for the record?

Mr. FOUNTAIN. Yes.

[The information may be found in the appendix at pp. 364–365.]

Mr. FOUNTAIN. I note that a labeling claim for use in upset stomach is made for Alka-Seltzer but the monograph does not permit such a claim.

Mr. HUTT. That is correct. That is a category III claim which, if they began testing within 6 months after the effective date, they

could continue to use. This was recommended by the advisory committee, for a 2-year period.

Mr. FOUNTAIN. So I assume the upset stomach claim in labeling for Alka-Seltzer constitutes compliance with regulation 331.30 specifying the allowable claims for antacid products?

Mr. HUTT. It constitutes compliance with two parts of the Commissioner's order; first, the monograph itself; second, the Commissioner's determination of OTC antacid drug product conditions for which the available data are insufficient to permit final classification at this time (category III) which appears on pages 19873 and the next page of the Federal Register of June 4, 1974.

Mr. FOUNTAIN. So for the next 2 years——

Mr. HUTT. One year now.

Mr. FOUNTAIN. One year now, on the basis of what you have done, the manufacturer is using a claim which is not in the monograph. Is that right?

Mr. HUTT. Yes. It is in category III and there is a 2-year transitional period during which they may, therefore, test the ingredient to prove the claim or delete it.

I might add, as you know, Mr. Chairman, that is not true of category II ingredients or claims. They are all deleted as of this date.

Mr. FOUNTAIN. In view of the requirements of the law, will you tell us what your authority is now under the law to sanction by regulation interstate shipments of a product which bears claims which are not authorized by the effective monograph?

Mr. HUTT. Yes, sir. This is pursuant to a transitional provision which has been authorized by the courts.

In the case of *American Public Health Association* v. *Veneman*, which was decided in 1972, the very question that you raised was considered. Judge Bryant, in his order published in the Federal Register of December 14, 1972, for prescription drugs gave a 4-year period of time during which we could implement the NAS/NRC review with regard to effectiveness.

Then in paragraph XV——

Mr. FOUNTAIN. A judge gave a 4-year period?

Mr. HUTT. Yes.

Mr. FOUNTAIN. On what basis?

Mr. HUTT. On the basis that that was a reasonable time period in the use of administrative discretion in implementing a statute which the judge realized could not be done overnight, just as this job cannot be done overnight.

Because of the particular issue of over-the-counter drugs he included the following paragraph in his order, paragraph XV, which appears on page 26624 of that issue of the Federal Register:

> Over-the-counter human drugs which are the subject of NAS–NRC reports shall be reviewed and handled pursuant to the procedure established in the Federal Register of May 11, 1972 (37 F.R. 9464 et seq.).

Mr. FOUNTAIN. That is for effectiveness.

Mr. HUTT. Yes. The upset stomach issue is not a safety issue.

Mr. FOUNTAIN. As a result we have had NDA's.

Mr. HUTT. An NDA "covers" any related or similar or identical drug whether it was on the market before or after the NDA, under the *USV* case.

In effect, what Judge Bryant was recognizing as a matter of law was that any regulatory statute is subject to reasonable interpretation and application in the exercise of administrative discretion and that in effect what we were doing was perfectly reasonable.

Mr. FOUNTAIN. I suggest that you, Mr. Goldhammer and Dr. Goldberg get together to find out what we have requested and what you have agreed to submit, and see whether you can reconcile the differences of opinion which seem to exist in connection with the contents of some of the documents to which we have made reference.

Mr. HUTT. We would be happy to do that, Mr. Chairman.

Mr. FOUNTAIN. We can make that part of the record.

Mr. HUTT. Yes, sir.

Mr. THOMPSON. One final comment. I think today marks the last official appearance of Mr. Hutt before this subcommittee as General Counsel of the FDA. While his appearances have at times been stormy I think we can all agree he has conducted himself in an extremely competent fashion.

The Congress and the Administration are currently working on the whole question of regulatory reform. While it is not within my competence to predict what will happen, I think a lot of the reforms you have brought to the Food and Drug Administration will in substance be transposed to the other regulatory agencies.

For that, on behalf of the minority members, I wish to congratulate you.

Mr. HUTT. Thank you, sir.

Mr. FOUNTAIN. I didn't realize this is your last day, Mr. Hutt. I want to wish you well. I would like to say that if I were going to employ counsel who was in a position to do a good job of explaining away the unexplainable and defending the positions you have taken, I would want you as my attorney; I would certainly not hesitate to employ you.

I want to wish you well in whatever you do and in whatever you undertake.

Mr. HUTT. Thank you, Mr. Chairman.

Mr. FOUNTAIN. The subcommittee stands adjourned, to reconvene subject to the call of the Chair.

[Whereupon, at 4:30 p.m., the subcommittee adjourned, to reconvene subject to the call of the Chair.]

55-495—75——17

APPENDIX

Additional Correspondence and Material Relative to the Hearings

During Subcommittee hearings in March, April, and May 1974, on "Use of Advisory Committees by the Food and Drug Administration", questions were raised concerning estimated costs submitted by the Food and Drug Administration to the Office of Management and Budget for FDA Advisory Committees and Panels for 1972 and 1973.

On October 31, 1974, Congressman Fountain received a letter from HEW Secretary Caspar W. Weinberger stating that FDA amendments to the figures for the President's Report submitted by FDA to OMB would be sent to the subcommittee when completed.

On June 11, 1975 FDA Commissioner Schmidt sent the amended cost data. [The documents referred to follow:]

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., October 31, 1974.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: Your letter of last July 15 inquired about cost estimates for certain Food and Drug Administration (FDA) advisory committees. These estimates were provided in the President's Annual Reports on Federal Advisory Committees for the calendar years 1972 and 1973, and varied considerably from data that you had obtained directly from FDA for the same committees. My response of August 15 indicated that the estimates in the President's Reports were made in advance of the years in question, without sufficient experience to rely upon.

After investigating the matter further, however, Dr. Alexander M. Schmidt, Commissioner of Food and Drugs, has informed me that the figures for the President's Reports could have been and should have been based on actual cost data rather than on rough estimates, as was the case. Thus, we would like to amend, for the record, the entire FDA portion of the President's Reports for 1972 and 1973. We will send you a copy of these amendments when they are completed.

After discussing this matter with Dr. Schmidt, I am convinced that the initial sets of figures provided for the annual report by FDA were not intended to misrepresent the facts. The errors resulted from inadequate attention to the requirements of the Advisory Committee Act and the preparation of these estimates outside the normal budget channel. Dr. Schmidt assures me that his Agency is taking steps to insure that costs for the current and future years are reported on an accurate and timely basis.

Sincerely,

(S) CASPAR W. WEINBERGER,
Secretary.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Rockville, Md., June 11, 1975.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations, Committee on Government Operations, House of Representatives, Washington, D.C. 20515

DEAR MR. FOUNTAIN: On October 31, 1974, Secretary Weinberger wrote to you concerning the matter of the Food and Drug Administration (FDA) advisory committee costs for calendar years 1972 and 1973 and stated that FDA would recalculate costs for those years and report actual cost data to you.

The amended FDA portion of the President's report to the Congress is enclosed.

Sincerely yours,

ALEXANDER M. SCHMIDT, M.D.,
Commissioner of Food and Drugs.

Enclosure.

	Committee members and consultant cost	Administrative support estimates	Special support costs	Total costs	(Original estimate)	Total FDA man-years	(Original estimate)
CALENDAR YEAR 1972							
(a) New advisory committees created in FDA during calendar year 1972 and whose creation was specifically directed by statute: None.							
(b) New advisory committees created by FDA during calendar year 1972 other than those specifically directed by statute:							
Dental Drug Products Advisory Committee				(1)			
Diagnostic Products Advisory Committee	$6,400	$5,700	$1,400	$13,500	($10,000)	0.3	(0.3)
Drug Experience Advisory Committee				(1)			
Panel on review of anesthesiology medical devices	3,700	5,800		9,500	(10,000)	.3	(.3)
Panel on review of antacids	23,200	36,800	7,400	67,400	(10,000)	1.9	(.3)
Panel on review of antimicrobial agents	38,200	30,800	11,100	80,100	(10,000)	1.6	(.3)
Panel on review of bacterial vaccines and bacterial antigens				(1)			
Panel on review of cardiovascular medical devices	4,500	5,800		10,300	(9,000)	.3	(.3)
Panel on review of cough, cold, allergy, bronchodilator and antiasthmatic drugs	5,700	11,500	1,700	18,900	(10,000)	.6	(.3)
Panel on review of dental medical devices	4,200	5,800		10,000	(10,000)	.3	(.3)
Panel on review of dentifrices and dental care agents				(1)			
Panel on review of internal analgesic agents	5,800	11,500	2,300	19,600	(10,000)	.6	(.3)
Panel on review of laxative, antidiarrheal, antiemetic, and emetic				(1)			
Panel on review of orthopaedic medical devices	7,900	5,800		13,700	(9,000)	.3	(.3)
Panel on review of sedative, tranquilizer and sleep aid drugs	4,700	5,800	500	11,000	(10,000)	.3	(.3)
Panel on review of topical analgesics				(1)			
Pulmonary-Allergy Clinical Immunology Advisory Committee	2,400	5,800	1,000	9,200	(9,000)	.3	(.3)
Total	106,700	131,100	25,400	263,200	(107,000)	6.8	(3.3)
(c) All advisory committees created by statute of by FDA and in existence at the end of CY 1972 except those listed in (a) or (b):							
Anti-infective Agents Advisory Committee	9,900	21,700		31,600	(9,000)	1.1	(.3)
Biometric and Epidemiological Methodology Advisory Committee	3,200	5,800	700	9,700	(7,000)	.6	(.3)
Board of Scientific Counselors				(2)			
Board of Tea Experts	700	300		1,000	(1,000)	.1	(.1)
Cardiovascular and Renal Advisory Committee	7,500	11,500	1,200	20,200	(9,000)	.6	(.3)
Dermatology Advisory Committee				(2)			
Endocrinology and Metabolism Advisory Committee				(2)			
FDA/NIMH Drug Abuse Advisory Committee	6,700	15,400		22,100	(10,000)	.8	(.3)
Medical Devices Advisory Committee	5,600	5,800		11,400	(9,000)	.3	(.3)
Medical Radiation Advisory Committee	7,800	11,500	4,500	23,800	(12,000)	.64	(.3)
National Advisory Committee on Consumer Product Safety				(4)			
National Advisory Drug Committee	21,200	17,700	2,100	41,000	(15,000)	.92	(.3)
National Advisory Food Committee	14,200	11,900	1,100	27,200	(15,000)	.62	(.3)
National Advisory Veterinary Medicine Committee				(2)			
Neuropharmacology Advisory Committee	16,500	16,300	1,500	34,300	(9,000)	.85	(.3)
Obstetrics and Gynecology Advisory Committee	7,000	11,500	1,000	19,500	(10,000)	.6	(.3)
Ophthalmic Drugs Advisory Committee	6,800	11,500	900	19,200	(9,000)	.6	(.3)
Poison Prevention Packaging Technical Advisory Committee	9,200	5,800		15,000	(15,000)	.3	(.3)
Radiation Bio-effects and Epidemiology Advisory Committee	4,900	6,700		11,600	(10,000)	.35	(.3)

Radioactive Pharmaceuticals Advisory Committee	6,400	12,500	100	19,000	(9,000)	.65	(.3)
Radiological Health Research and Training Grants Review Committee	2,200	3,800		6,000	(6,000)	.3	(.3)
Respiratory and Anesthetic Drugs Advisory Committee	4,200	5,800		10,000	(9,000)	.3	(.3)
Surgical Drugs Advisory Committee	2,800	5,800	600	9,200	(9,000)	.3	(.3)
Technical Electronic Product Radiation Safety Standards Committee	5,400	5,800	1,700	12,900	(10,000)	.3	(.3)
Total	142,100	187,100	15,400	344,600	(183,000)	10.23	(5.4)
(d) All advisory committees terminated during calendar year 1972:							
Methadone Maintenance Advisory Committee				(3)			
Food Standards Committee				(2)			
1972 total, all committees	248,800	318,200	40,800	607,800	(290,000)	17.03	(8.7)

CALENDAR YEAR 1973

(a) New advisory committees created in FDA during calendar year 1973 and whose creation was specifically directed by statute: None.

(b) New advisory committees created in FDA during calendar year 1973 other than those specifically directed by statute:

Controlled Substance Advisory Committee				(1)			
Oncologic Drugs Advisory Committee				(1)			
Panel on review of allergenic extracts				(1)			
Panel on review of antiperspirant drug products				(1)			
Panel on review of bacterial vaccines and toxoids	16,500	18,400		34,900	(45,000)	.9	(.3)
Panel on review of blood and blood derivatives				(1)			
Panel on review of contraceptives and other vaginal drug products	15,800	18,500		34,300	(15,000)	.9	(.3)
Panel on review of ear, nose, and throat devices				(1)			
Panel on review of gastroenterology and urological devices				(1)			
Panel on review of general hospital devices				(1)			
Panel on review of general and plastic surgery devices				(1)			
Panel on review of hemorrhoidal drugs	24,700	18,500		43,200	(15,000)	.9	(.3)
Panel on review of immune serums, antitoxins and antivenins				(1)			
Panel on review of in vitro diagnostic reagents				(1)			
Panel on review of miscellaneous biological products				(1)			
Panel on review of miscellaneous external drug products				(1)			
Panel on review of miscellaneous internal drug products				(1)			
Panel on review of neurology devices				(1)			
Panel on review of obstetrics and gynecology devices				(1)			
Panel on review of ophthalmic devices				(1)			
Panel on review of ophthalmic drugs	12,500	12,300		24,800	(15,000)	.6	(.3)
Panel on review of oral hygiene drug products				(1)			
Panel on review of pathology devices				(1)			
Panel on review of physiatry devices				(1)			
Panel on review of radiology devices				(1)			
Panel on review of skin test antigens				(1)			
Panel on review of viral vaccines and rickettsial vaccines	14,100	18,500		32,600	(45,000)	.9	(.3)
Panel on review of vitamin, mineral, and hematinic drug products	4,000	6,100		10,100	(15,000)	.3	(.3)
Science Advisory Board—National Center for Toxicological Research	4,800	6,100	500	11,400	(45,000)	.3	(.2)
Total	92,400	98,400	500	191,300	(195,000)	4.8	(2.0)

See footnotes at end of table.

	Committee members and consultant cost	Administrative support estimates	Special support costs	Total costs	(Original estimate)	Total FDA man-years	(Original estimate)
CALENDAR YEAR 1973—Continued							
(c) All advisory committees in existence at the end of calendar year 1973 except those listed in (a) or (b) above:							
Anti-Infective Agents Advisory Committee	$9,600	$23,300		$32,900	($13,000)	1.1	(0.3)
Biometric and Epidemiological Methodology Advisory Committee	4,700	12,300	$2,200	19,200	(11,000)	.6	(.2)
Board of Tea Experts	700	300		1,000	(2,000)	.1	(.1)
Cardiovascular and Renal Advisory Committee	12,100	30,900	3,000	46,000	(13,000)	1.5	(.3)
Dental Drug Products Advisory Committee	6,400	12,300	3,000	21,700	(13,000)	.6	(.3)
Dermatology Advisory Committee	1,400	6,100	600	8,100	(13,000)	.3	(.3)
Diagnostic Products Advisory Committee	34,100	18,400	3,000	55,500	(14,000)	.9	(.3)
Drug Experience Advisory Committee	7,300	12,300	2,700	22,300	(15,000)	.6	(.3)
Endocrinology and Metabolism Advisory Committee	8,900	12,300	3,900	25,100	(13,000)	.6	(.3)
FDA/NIMH Drug Abuse Advisory Committee	7,400	16,400		23,800	(15,000)	.8	(.3)
Medical Devices Advisory Committee				(0)			
Medical Radiation Advisory Committee	5,700	6,200	1,300	13,200	(16,000)	.3	(.3)
National Advisory Drug Committee	13,600	16,800		30,400	(19,000)	.82	(.3)
National Advisory Food Committee	13,600	17,000		30,600	(19,000)	.83	(.3)
National Advisory Veterinary Medicine Committee	19,300	16,800		36,100	(16,000)	.82	(.3)
Neuropharmacology Advisory Committee	18,300	17,400	7,700	43,400	(13,000)	.85	(.3)
Obstetrics and Gynecology Advisory Committee	15,800	28,400	5,500	49,700	(20,000)	1.4	(.5)
Opthalmic Drugs Advisory Committee	11,900	12,300	2,900	27,100	(13,000)	.6	(.5)
Panel on review of anesthesiology devices	15,600	12,300		27,900	(14,000)	.6	(.3)
Panel on review of antimicrobial agents	44,700	41,000	17,400	103,100	(15,000)	2.0	(.3)
Panel on review of antacids	2,300	2,100	900	5,300	(15,000)	.1	(.3)
Panel on review of bacterial vaccines and bacterial antigens	33,900	41,000		74,900	(23,000)	2.0	(.3)

Panel on review of cardiovascular devices	12, 100	16, 400		28, 500	(14, 000)	.8	(.3)
Panel on review of cold, rough, allergy bronchodilator and antiasthmatic agents	35, 500	41, 000	12, 800	89, 300	(15, 000)	2.0	(.3)
Panel on review of dental devices	18, 000	18, 500		36, 500	(14, 000)	.9	(.3)
Panel on review of dentifrices and dental care agents	31, 900	28, 700	1, 400	52, 000	(15, 000)	1.4	(.3)
Panel on review of internal analgesic including antirheumatic drugs	35, 000	41, 000	14, 800	90, 800	(15, 000)	2.0	(.3)
Panel on review of laxative, antidiarrheal, antiemetic and emetic drugs	29, 300	18, 400		47, 700	(15, 000)	.9	(.3)
Panel on review of orthopaedic devices	11, 500	12, 300		23, 800	(14, 000)	.6	(.3)
Panel on review of sedative, tranquilizer, and sleep aid drugs	49, 400	30, 800	1, 000	81, 200	(15, 000)	1.5	(.3)
Panel on review of topical analgesics including antirheumatic, otic, burn, sunburn, treatment and prevention drugs	21, 500	30, 700	6, 700	58, 900	(15, 000)	1.5	(.3)
Pulmony-Allergy and Clinical Immunology Advisory Committee	5, 800	12, 300	2, 500	20, 600	(13, 000)	.6	(.3)
Radiation Bio-effects and Epidemiology Advisory Committee	4, 500	11, 300	1, 100	16, 900	(14, 000)	.55	(.3)
Radioactive Pharmaceuticals Advisory Committee	7, 600	13, 300	1, 000	21, 900	(14, 000)	.65	(.5)
Respiratory and Anesthetic Drugs Advisory Committee	5, 300	6, 100	1, 600	13, 000	(13, 000)	.3	(.3)
Surgical Drugs Advisory Committee	11, 000	12, 300	2, 400	25, 700	(13, 000)	.6	(.3)
Technical Electronic Product Radiation Safety Standards Committee	10, 900	12, 300	3, 600	26, 800	(14, 000)	.6	(.5)
Total	576, 600	661, 300	103, 000	1, 340, 900	(500, 300)	32. 32	(11. 3)
All advisory committees terminated during calendar year 1973 including those terminating Dec. 31:							
Board of Scientific Counselors				[2]			
National Advisory Committee on Consumer Product Safety				[4]			
Radiological Health Research and Training Grants Review Committee	4, 200	5, 800		10, 000	(10, 000)	.3	(.3)
Total	4, 200	5, 800		10, 000	(10, 000)	.3	(.3)
1973 total, all committees	673, 200	765, 500	103, 500	1, 542, 200	(723, 000)	37. 42	(13. 6)

[1] Established but did not meet during report year. No costs were associated with establishment.
[2] Inactive committee transferred to FDA by reorganization of 1972. Committee was abolished Mar. 7, 1973.
[3] Did not meet during report year.
[4] Established 1971 and staffed during 1972. Committee never met due to transfer of product safety program from FDA to the newly-created Consumer Product Safety Commission in May 1973. Committee was subsequently abolished. No costs were associated with establishment and staffing.
( ) = Estimates originally submitted to Office of Management and Budget by FDA.

PLOUGH, INC.,
Memphis, Tenn., December 29, 1972.

Subject: OTC Review—DI-GEL.

ALAN KAPLAN, Esq.
Kleinfeld & Kaplan, Sunderland Building, 1320 Nineteenth Street, N.W., Washington, D.C.

Dear ALAN: Enclosed is our letter on the subject to FDA's Yingling, dated December 29 and signed by Harry Feinstone. I understand that upon receipt you will hand deliver promptly to Yingling or if he is unavailable, to one of his top assistants, and that you will give us a call when this is done.

Many thanks for your help. Your input made this a significantly stronger document.

I am also enclosing three photocopies for your convenience. I leave to you the question of whether Yingling should be given more than one copy or whether anyone else at FDA should be given a copy by us.

Sincerely,

FRANK P. DIPRIMA,
Secretary and Legal Director.

Enclosures.

PLOUGH, INC.,
Memphis, Tenn., December 29, 1972.

GARY L. YINGLING, Esq.
Director, OTC Drug Products Evaluation Staff, Office of Scientific Evaluation, Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Md.

DEAR MR. YINGLING: We have received a copy of a draft of a proposed report and recommended monograph ("the Draft") covering antacid preparations. The Draft was covered by your memorandum of December 22, 1972, to "Members of OTC Antacid Review Panel and Industry Liaison." The Draft, as we understand it, was prepared by Food and Drug Administration's OTC Review Staff to embody conclusions and recommendations of the Advisory Review Panel on Over-The-Counter Antacids. We are writing concerning those elements of the Draft which relate to the antigas ingredient Simethicone.

The Draft categorizes Simethicone as an ingredient for which available data is insufficient to permit final classification at this time. The Draft recognizes the safety of the ingredient, but would provide a two year period to develop and submit further data regarding efficacy.

We respectfully submit that certain of the views expressed in the Draft, as they relate to Simethicone, appear to have been framed without full consideration of much of the data before the Panel. This is understandable in view of the great volume of information submitted to the Panel from many sources on many ingredients.

We respectfully request an opportunity to meet with appropriate representatives of Food and Drug Administration to discuss the comments made in this letter in more detail. We would have addressed our request for such a meeting directly to the Panel, but it is our understanding that the Panel does not plan to meet again.

In response to a request for views and data on antacid products, published in the Federal Register of January 5, 1972, Plough, Inc., delivered to your offices on February 4 eight copies of a submittal on its products, DI-GEL Tablets and Liquid, which are combinations of commonly used antacids with the antigas ingredient Simethicone. We understand that submittals such as ours formed part of the basic source material for the Panel; we also understand that your office retained a copy of the submittal. Thus, for convenience, we have not given detailed official citations but instead have cited page numbers in our submittal.

BACKGROUND—RATIONALE FOR SIMETHICONE-ANTACID COMBINATION

The rationale for the use of Simethicone in combination with antacids in self-medication products may be simply stated as follows: Sufferers of functional gastric disturbance, whether denominated as "heartburn," "sour stomach" or "acid indigestion," are often actually suffering from gaseous accumulations instead of, or in addition to, hyperacidity. (The symptoms may indeed exist in the absence of hyperacidity or even with hypoacidity or achlorhydria.) Such gaseous accumulations may cause, or contribute to, or accompany, the esophageal reflux which the Draft recognizes is often the true cause of "heartburn," "sour stomach"

or "acid indigestion." This appears to be well recognized. Feelings of fullness and bloating often also accompany this generalized gastro-intestinal functional disturbance, and are often also caused by gas. This too is well recognized.[1] Thus, even though the Draft states that claims which link symptoms such as "full feeling" and "gas" with gastric acidity are dubious (and this is consistent with our position), the Draft does not deny that these symptoms commonly exist. We agree with the Panel that lay sufferers may not be able to distinguish between many of these various vague symptoms so as to be able to draw valid conclusions as to their cause or intermediation. However, a product which combines antacids with an effective antigas agent is likely to provide relief from the functional gastric or gastro-intestinal disturbance, whether it is caused by conditions successfully treated by antacids, or caused by gaseous accumulations, or by both. And, where the antigas ingredient does not add a risk factor, as the Panel recognizes is the situation with Simethicone, the combination is a truly rational one.

THE DRAFT—COMMENTS ON EFFECTIVENESS

We have restated the rationale for a Simethicone-antacid combination. We now turn to the Panel's expressed uncertainty regarding the effectiveness of Simethicone.

The Draft states that the Panel recognizes that the addition of an antifoaming agent, such as Simethicone, to antacids provides the product with antifoaming characteristics. The Draft further states that it is "reasonably certain" that Simethicone causes small gas bubbles to coalesce and form larger ones, but that it has not been "clearly demonstrated" that this change is clinically beneficial. At the same time the Panel concludes that controlled studies do show a lessening of post-operative gas pains and of gaseous accumulation with Simethicone but that studies concerning gas accumulation under the ordinary conditions of life under which OTC antacids are normally used were limited and not well controlled. The Draft also indicates that many lay sufferers complaining of "gas" may not have gaseous accumulations.

As indicated in the preceding paragraph, the Panel questioned the efficacy of Simethicone on three grounds:

(1) Uncertainty that coalescence of bubbles is beneficial;

(2) That studies respecting gas accumulation "under ordinary conditions of life . . . are limited and not well controlled"; and

(3) Uncertainty that "many of the sensations of 'gas' of which patients complain are actually produced by accumulations of gas."

These three questions are discussed below.

(1) Is Coalescence of Bubbles Beneficial?

In direct contrast to the uncertainty expressed in the Draft, the authoritative publication, *AMA Drug Evaluations, 1971*, 1st Edition, states flatly, in its section on Simethicone:

"Coalescence of bubbles facilitates elimination of gas." [2]

Once mucus-imbedded bubbles are broken or coalesced, gas is liberated from its entrapped state, and the free gas thus formed, like any other free gas, passes more easily from one area to another. It is thus more easily eliminated through belching or passing flatus, thereby relieving symptoms generally associated with gas accumulation. The mode of action of Simethicone is described by Rider,[3] among others.

(2) Studies Submitted

Several controlled studies submitted found Simethicone efficacious against functional distress due to gas accumulation. In a double-blind study by Marks, et al,[4] of 32 patients with functional disturbance, 25 obtained relief with Simethicone, and the Simethicone-induced remission was maintained in only 5 of those subjects after they were switched to placebo; placebo was preferred in only one of the 32 subjects. Similarly, in a controlled study reported by Oswald,[5] Simethi-

[1] See *Merck Manual, Twelfth Edition*, pp. 679–682 for an example of an authoritative source recognizing the prominent role of gas in generalized functional dyspepsia, "indigestion" and functional gastro-intestinal disturbance.

[2] Plough, Inc., *Submittal To Panel On Antacid Products*, DI-GEL Liquid, DI-GEL Tablets (February 4, 1972), p. 330.

[3] Ibid., p. 259 at 263.

[4] Ibid., p. 250.

[5] Ibid., p. 254.

cone and a Simethicone-antacid combination produced excellent to good results in 65% of the 70%, respectively, of the subjects tested, compared with 36% for placebo. Rider [6] reported that 84 of 117 subjects, subjects with functional disturbance obtained good to excellent results from Simethicone; 20 of the 84 were then switched to placebo, and in 18 cases, symptoms returned. Similar results were reported by Rider and Moeller [7] for an even larger test population. Slanger [8] tested an antacid-Simethicone combination in two groups of patients, one with functional disturbance, another with organic disturbance; overall clinical response was 84% good or excellent in the functional group, 75% in the organic group. In a study by Hock,[9] ulcer and functional gastritis patients were given an antacid-Simethicone preparation substantially identical to DI-GEL Tablets; symptoms were significantly reduced in 80% of the patients given the Simethicone-antacid preparation, but when these patients were switched, without their knowledge, to the antacid alone, 44% complained of a worsening of their symptoms. Thus, the antacid-antigas combination provided greater relief than the antacid alone.

There is thus a great deal of evidence from controlled and partially controlled studies to the effect that Simethicone is effective "under ordinary conditions of life," i.e., against functional disturbance. This is powerfully corroborated by many highly objective photographic studies showing a lessening of accumulations of gas.[10] Not all of these X-ray studies involved post-operative conditions. Hoon [11] reported excellent results on patients with mild gastritis. Ausman [12] also reported a dramatically decreased amount of accumulated gas, as judged photographically, in patients being prepared for abdominal X-rays. Gasster, et al.,[13] and Garry [14] both reported similarly excellent results on patients other than post-operative patients.

Additionally, the several controlled studies acknowledged by the Draft, and therefore not cited here, proving Simethicone effective at lessening post-operative gas pains, cannot be lightly dismissed. The essential element is that gas pains and gas accumulation were lessened. These studies further corroborate the evidence discussed herein.

Thus, the activity and effectiveness of Simethicone has been proven: (i) in controlled and partially controlled studies in patients with functional disturbances including a controlled study comparing a Simethicone-antacid combination with an antacid alone; (ii) in highly objective photographic studies of normal patients and those with mild gastritis; (iii) in highly objective photographic studies on post-operative patients; and (iv) in controlled clinical studies showing lessening of gas pains in post-operative patients. We submit that efficacy has been so amply proven that a requirement that further studies be performed over the next two years would be superfluous and wasteful of scientific resources.

The safety of Simethicone has been established beyond question, and has been accepted in the Draft, and for these reasons it has not been discussed at any length in this letter. We call your attention, however, to the relevance of safety to the regulation's definition of efficacy. The regulation at Section 130.301(a)(4)(iii) indicates that the benefit-to-risk ratio is material to a determination of effectiveness as well as safety. Thus, a finding of effectiveness would be supported not only by all of the efficacy data, adduced above, but also by Simethicone's extraordinary safety data and safety record.

(3) Incidence of Gas in Subjects Complaining of "Gas"

Certainly, we do not claim that all patients complaining of "gas" actually are suffering from gaseous accumulations. Under the regulation at Section 130.31(a)(4)(ii), it is sufficient that a nonprescription drug be effective "in a significant proportion of the target population." In this case the target population consists of sufferers of functional gastrointestinal disturbances.

The medical literature is replete with statements that gas is a leading cause of such disturbances. Hock [15] states that flatulence "heads the list of symptoms

[6] Ibid., p. 259.
[7] Ibid., p. 265.
[8] Ibid., p. 390.
[9] Ibid., p. 466.
[10] Ibid., p. 302, 309, 317, 322, 325, 364, 373 and 469.
[11] Ibid., p. 309.
[12] Ibid., p. 302.
[13] Ibid., p. 325.
[14] Ibid., p. 322.
[15] Ibid., p. 466 at 467.

referable to the abdominal area." Rider[16] reports that bloating, gaseous distension and excessive gas are "among the most common complaints of patients attending a gastroenterology clinic." Pellegrino and Silberman[17] state that "all persons experience occasional gas discomfort or distress." According to Slanger[18] "the two most common complaints referable to the gastrointestinal tract for which patients seek medical advice are hyperacidity and gas. The two often occur together." Berkowitz et al.,[19] state that "intestinal gas with its various manifestations is probably the most common problem encountered in clinical practice." Lieberthal and Frank state that one of the common causes of symptoms referable to the gastrointestinal tract is gaseousness.[20] There are dozens of other authoritative statements to the same effect in our submittal.

Lay sufferers of course may not distinguish between the various vague manifestations of functional indigestion, classified by the Panel as "heartburn," "sour stomach" and "acid indigestion." Clearly, a "significant portion" of those suffering from common functional indigestion or dyspepsia are suffering from gas accumulations, alone or with other symptomatology.[21]

* * * * * * *

Principally, the monographs are intended to define what is generally recognized as safe and effective. Safety of Simethicone and the safety and effectiveness of the antacids have been accepted by the Panel. The issue thus boils down to whether Simethicone is generally recognized as effective as an adjunct to antacid therapy in self-medication.

The evidence is overwhelming that Simethicone is so generally recognized as effective. It has been accepted by the authoritative AMA Drug Evaluations, 1971.[22] The National Formulary's committee on admissions has designated Simethicone as an addition to its 1975 edition. Simethicone will be categorized as an antiflatulent. The Committee only designates ingredients which it finds to have demonstrated efficacy. Certain Simethicone-antacid preparations (similar to DI-GEL) promoted solely to the medical profession and not to the lay public sold in excess of 35,000,000 package units in 1971,[23] and the rate is substantially higher for 1972. Since there is no consumer advertising for these preparations, their wide use can be attributed to recommendations of physicians who have experienced success with them. The ingredient has been used consistently and successfully in the space program. There are about two dozen published studies supporting its efficacy, alone and in combination with antacids.

For all of the reasons stated above, we urge FDA to include Simethicone in the forthcoming proposed monograph as an ingredient recognized as safe and effective for use in combination with antacids for relief of the symptoms of heartburn, sour stomach and acid indigestion (whether or not attributable to normal or hypernormal gastricacidity), and of bloating, flatulence, pressure and fullness. We respectfully request that a meeting be scheduled to permit our representatives (including scientific representatives with expertise in the field of gastroenterology) to discuss in greater detail the contents of this letter with representatives of the Food and Drug Administration.

Respectfully,

W. Harry Feinstone, Sc. D.,
Vice President, Scientific Affairs.

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[16] Ibid., p. 186.
[17] Ibid., p. 210.
[18] Ibid., p. 221.
[19] Ibid., p. 246.
[20] Ibid., p. 280.
[21] See also, footnote 1, this letter.
[22] Plough, Inc., *supra*, p. 330. The section on Simethicone states, in part: ". . . Coalescence of bubbles facilitiates elimination of gas. [Simethicone] may help patients exhibiting the many vague symptoms of excessive aerophagia (e.g., bloating, dyspepsia, borborygmi, flatulence, eructation, anorexia, constipation). . . . Some Simethicone preparations also contain antacids which is therapeutically defensible."
[23] Ibid., pp. 11 and 228.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 310, 700]

AEROSOL DRUG AND COSMETIC PRODUCTS CONTAINING ZIRCONIUM

Notice of Proposed Rule Making

The Commissioner of Food and Drugs proposes to determine that any aerosol drug or cosmetic product containing zirconium is a new drug or an adulterated cosmetic. Interested persons have until September 3, 1975 to submit comments.

Pursuant to procedures promulgated in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), a review of the safety and effectiveness of over-the-counter (OTC) drugs has been undertaken by the Food and Drug Administration (FDA).

Notice inviting submission of data and information, published and unpublished, and other information pertinent to the safety and effectiveness of OTC antiperspirant products was published in the FEDERAL REGISTER of September 7, 1973 (38 FR 24391). The Panel on Review of Antiperspirant Drug Products has reviewed the submissions of data and other information regarding the use of antiperspirant products containing zirconium.

The Commissioner of Food and Drugs received, on April 29, 1975, a report of the OTC Antiperspirant Panel on aerosol antiperspirants containing zirconium.

In its report, the Panel indicates that the benefit from using drug and cosmetic aerosol products containing zirconium is insignificant when compared to the risk. The Panel notes that zirconium-containing aerosol antiperspirants are not more effective than non-aerosolized antiperspirants containing zirconium or aluminum salts. The Panel further states that there is little evidence that consumers can perceive a difference between any of the aerosolized or nonaerosolized products under conditions of actual use. The Panel concludes that there is so little benefit to be derived from the use of zirconium-containing aerosol antiperspirants when there are far safer aerosolized and nonaerosolized antiperspirants, that it is unjustified to subject even a few individuals to such a risk.

On the basis of the Panel's report, the Commissioner tentatively concludes that aerosol products containing zirconium cannot be considered generally recognized as safe (GRAS) for use in drug and cosmetic products.Therefore, he proposed that any drug product containing zirconium in an aerosol form should be classifies as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)), implemented by § 310.3(g) and (h)(5) (21 CFR 310.3(g) and (h)(5)). Section 310.3(h)(5) states "The newnesss of a drug may arise by reason (among other reasons) of: (5) The newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug." The Commissioner has reached this tentative conclusion because of the above noted safety issues in the Panel's report and because the aerosolized form of zirconium was not on the market in 1962 as required under section 107(c)(4) of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act (Pub. L. 87–781 (21. U.S.C. 321 note)) in order to qualify for exemption from the amendments. Under this proposal, any zirconium-containing aerosol antiperspirant will, therefore, be considered a new drug for which a new drug application (NDA) pursuant to section 505 of the act and Part 314 (21 CFR Part 314) is required.

The Commissioner, based upon the same safety considerations, also proposes that aerosol products containing zirconium are deleterious substances which may render any cosmetic product injurious to users. Accordingly, any such cosmetic product would be deemed to be adulterated under section 601(a) of the act.

Although the Panel's report concerned itself only with aerosol antiperspirants containing zirconium, the Commissioner is of the opinion that, without evidence to the contrary, no aerosol drug or cosmetic product containing zirconium can be considered as generally recognized as safe. Therefore, the Commissioner tentatively concludes that the proposed regulation shall extend to any aerosol drug or cosmetic product containing zirconium including, but not limited to, antiperspirants.

The Panel recommends that action to remove aerosol products containing zirconium be implemented expeditiously and not await the full procedural review

that has been established for OTC drug products in § 330.10 (21 CFR 330.10). Accordingly, on the basis of the Panel's concerns, the lack of toxicologic data adequate to the establishment of a safe level for use, the availability of other safer agents, the adverse benefit-to-risk ratio, and the recommendation for prompt action to remove these products from all drug and cosmetic products, the Commissioner has determined that the action he proposes regarding the use of these zirconium-containing aerosol products shall be taken through this notice of proposed rule making. The Commissioner tentatively has concluded that any delay in action regarding the use of these drug and cosmetic products is unjustified in view of the Panel's report and the evidence now at hand that such use cannot be generally recognized as safe and is contrary to the public interest.

However, because the major safety issue is attributable to prolonged use, the Commissioner at this time does not anticipate that a recall of previously marketed zirconium-containing aerosol drug and cosmetic products is necessary to protect the public health. It is the intention of the Commissioner that the effective date of the final regulation will be 30 days after publication in the FEDERAL REGISTER. Accordingly, under the provisions of this proposal, such products shipped in interstate commerce after the effective date of the final regulation which are not in compliance with the regulation will be regarded as not an approved new drug or, if the product is a cosmetic, as adulterated under section 601(a) of the act and subject to regulatory action.

If published as proposed, the final regulation regarding the use of these zirconium-containing aerosol products will apply to all drug and cosmetic products until such time as new evidence on their safety results in amendment of a monograph to be established for OTC antiperspirant products pursuant to the OTC drug review procedures under § 330.10.

In accordance with § 330.10(a)(2), all data and information concerning OTC zirconium-containing aerosol antiperspirant drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and the Food and Drug Administration. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before July 7, 1975, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to the Food and Drug Administration, Bureau of Drugs, Division of OTC Drug Evaluation (HFD–510), 5600 Fishers Lane, Rockville, MD 20852.

The conclusions and recommendations contained in the April 29, 1975 report of the Advisory Review Panel on OTC Antiperspirant Drug Products for antiperspirant products containing zirconium are as follows:

The Commissioner appointed the following panel to review the data and information submitted, and to prepare a report on the safety and effectiveness and labeling of OTC antiperspirant drug products pursuant to § 330.10(a)(1):

E. William Rosenberg, M.D., Chairman; J. Wesley Clayton, Ph.D.; Charles A. Evans, M.D., Ph.D.; Zenona Wanda Mally, M.D.; Jane M. Rosenzweig, M.D.; Robert J. Scheuplein, Ph.D.; and Eli Shefter, Ph.D.

The Panel was first convened on March 15, 1974 in an organizational meeting. Working meetings have been held on April 25–26, July 9–10, August 8–9, September 19–21, October 31 to November 2, December 16–17, 1974, and January 30–31, March 24–25, and April 24–25, 1975.

Two non-voting liaison representatives serve on the Panel, Ms. Marsha Gardner, nominated by an ad hoc group of consumer organizations and Robert Giovacchini, Ph.D., nominated by the Cosmetic, Toiletry and Fragrance Association.

Ms. Mary Bruch, an employee of the Food and Drug Administration, serves as Executive Secretary to the Panel. Lee Geismar, an employee of the Food and Drug Administration, serves as Panel Administrator, Gary Trosclair, R.Ph., served as Drug Information Analyst until November 1974 followed by Joe Hussion, R.Ph.

In addition to the Panel members and liaison representatives, the Panel has utilized the advice of the following consultants:

Dov Boros, Ph.D.; George Comstock, M.D.; Helen Dickie, M.D.; Robert Drew, Ph.D.; William Epstein, M.D.; Robert Jones, M.D.; Michael Lebowitz, M.D.; Lollie Marchant; W. G. Spector, M.D.; and Irwin Stolloff, M.D.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or the Panel's request:

Harold Baer, Ph.D.; Edwin V. Buehler, Ph.D.; Robert Choate; Ron Crytal, M.D.; Kenneth Ericson; Leon Golberg, M.D., D.Sc., Ph.D.; Leonard Harber, M.D.; Lester B. Hardy, Ph.D.; Clark Hoffman, Ph.D.; and Herman Jass, Ph.D

Frank Johnson, M.D.; William Jordan, M.D.; Albert M. Kligman, M.D.; Adalbert Koestner, D.V.M., Ph.D.; Edwin Larsen, Ph.D.; Bertil Magnusson, M.D.; Henry C. Maguire, Jr., M.D.; Howard I. Maibach, M.D.; Joseph Page, Esq.; Herbert Stokinger, Ph.D.; Hans Weill, M.D.; and Ronald Wulf, Ph.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through April 25, 1975, in arriving at its conclusions and recommendations.

The purpose of the OTC Antiperspirant Panel is to advise the Food and Drug Administration on the safety and effectiveness of currently marketed OTC antiperspirant drug products.

The Commissioner of Food and Drugs has stated that because self-medication is essential to the nation's health care system, it is imperative that over-the-counter drugs be safe, effective and adequately labeled. He further stated, "FDA accepts as necessary and desirable the tradition of self-medication . . . The consumer in turn has every right to expect that the OTC drugs he buys are safe and well labeled, and that they will perform as the manufacturer claims."

One of the specific charges to the Panel is: "To make recommendations to the Commissioner of Food and Drugs regarding those agents, their amounts, and combinations thereof, which based upon the available data, are not considered safe and effective . . ." The Panel acting under this charge has sent to the Commissioner its recommendation of March 25, 1975 that zirconium-containing aerosol antiperspirants be placed in OTC Category II and that appropriate steps be taken to withdraw these agents from interstate commerce until the safety testing adequate to secure the approval of an NDA has been performed.

The Panel has prepared the following in further explanation and support of these recommendations:

A. GUIDELINES

The Panel's recommendations were made within the framework of the following regulations pursuant to the OTC drug review procedures identified in § 330.10.

1. *Safety.* Means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under indications of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data (Ref. 1).

2. *Effectiveness.* Means a reasonable expectation that in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.111(a)(5)(ii) (21 CFR 314.111(a)(5)(ii)), unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data (Ref. 1).

3. *The benefit-to-risk ratio.* The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness, and further, as stated in paragraph 62 of the preamble to the final order establishing the procedures for classification of OTC drugs published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), "any drug which claims to be effective must have some pharmacologic action whether it is beneficial, aggravates an already existing condition, or results in an adverse reaction or side effect. In every instance the Panel must evaluate whether, balancing the benefits against the risks, the target population will experience a beneficial rather than a detrimental effect. Where little or no benefit is obtainable, of course, little or no risk is acceptable" (Ref. 1).

4. *General recognition of safety.* Only those drugs that are generally recognized as safe and effective and that are not misbranded may be lawfully marketed without an NDA. In § 330.10(a)(4)(i) the basis for general recognition is stated: "General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data."

The Panel has been charged with making the determination of whether or not specific antiperspirant drug products are generally recognized as safe and effective and not misbranded. The judgment of the Panel has been based on the following criteria: (a) factual information available from the scientific literature; (b) factual information available from FDA, from manufacturers of antiperspirant drug products, from producers of raw materials which are used in antiperspirant drug products and from companies engaged in testing antiperspirant drug products; (c) the informed judgment of knowledgeable experts testifying at open sessions of the Panel; and (d) the experience and informed judgment of the Panel members themselves.

B. OTHER ATTRIBUTES OF ANTIPERSPIRANT DRUG PRODUCTS

The Panel's charge with respect to both effectiveness and risk-benefit is to consider the "pharmacological effect of the drug"; for antiperspirant drug products, this is the antiperspirant action as measured by the degree of inhibition of axillary sweating.

The Panel has therefore concluded that the aesthetic attributes of the product per se or any other characteristics of the product per se that do not bear directly on the safety claims or efficacy are not relevant to this discussion. Such characteristics were considered only in terms of their impact on the overall safety or on the effectiveness of the antiperspirant drug product.

The specific form of the antiperspirant (aerosol, cream, lotion, or roll-on) or its method of application (by aerosol spray, by spray, by applicator or by hand) was considered when it related directly to safety or effectiveness.

C. RISK-BENEFIT AND THE SAFETY OF THE ANTIPERSPIRANT DRUG PRODUCTS

The Panel is specifically charged with balancing risk and benefit in its determination of the safety and effectiveness of antiperspirant drug products. The Panel has concluded that if a significant benefit is obtained by the users of effective antiperspirant drug products, some degree of risk is acceptable.

The degree of risk considered acceptable in the use of an antiperspirant is a matter of judgment. Some insight into the Panel's judgment on this matter may be found in its consideration of the topical zirconium-containing antiperspirants.

The Panel recognized distinct differences in the safety of topically applied versus aerosolized zirconium-containing compounds. Many adverse reactions to topically applied antiperspirant formulations include reports of irritation, stinging, rashes, boils, lumps and other manifestations of allergic and nonallergic contact dermatitis. Nonetheless, the Panel has tentatively agreed on the safety of topically applied, nonaerosolized, zirconium-containing antiperspirants because:

1. *Adverse reaction.* These adverse reactions are ordinarily not serious and are reversible.

2. *Site of reaction.* These reactions occur locally at the site of application where they are to be expected, where they are visible and where, once detected, they can be treated and the product discontinued.

3. *Incidence.* The incidence of such adverse reactions is extremely low, of the order of 6 per million units sold.

4 *Body burden.* Because these are applied topically, the entrance of zirconium-containing particles into the body is reduced virtually to zero when the skin's barrier is intact.

5. *Effectiveness.* This topically applied antiperspirant is reasonably effective.

6. *Misuse.* The Panel recommends that adequate labeling be provided to warn against applying the product to open, broken or abraded skin where the skin's barrier is breached. But even if this warning is ignored by the consumer, and the product is misused, the Panel believes the consequences will not be unreasonably severe.

The Panel believes that the risks of the non-aerosolized product are inherent in the effective use of the drug and are therefore unavoidable; other topically applied, nonaerosolized antiperspirants give comparable adverse reactions. Overall, the impact of these adverse reactions on the health of the target population is not large: these reactions are ordinarily not serious, they are reversible and their incidence is extremely low.

The Panel has not addressed the question of whether or not the ability to reduce underarm perspiration is an important social or occupational problem. The desirability of using antiperspirant drug products for this purpose is regarded as a personal decision by the individual consumer.

D. ALTERNATIVE CONVENIENCE FORMS AND RISK-BENEFIT

It is possible that antiperspirant drug products which are proven equally effective may not be judged equally safe It may happen that a larger degree of risk is incurred by the use of an alternative convenience form of the product; e.g., a different method of application or a different formulation with the same active ingredient. Such alternative forms may be designed to achieve a more acceptable product, a product of greater convenience, or simply one with greater consumer appeal. The Panel concludes that adequate safety may be a reasonably broad area which defines an equally broad area of minimal risk. As long as the safety of the product is considered adequate, in terms of the benefit achieved by its use, there would seem no need to insist that only the single safest form be marketed.

However, the Panel believes it is appropriate to consider comparative safety or the safety offered by alternative forms of the product when a substantial question of safety exists in a specific "convenience form." An alteration in the form of a drug product which may substantially compromise its safety without offering a compensating improvement in effectiveness seems to the Panel to be an instance where the following comment applies: "Where little or no benefit is obtainable, of course, little or no risk is acceptable" (Ref. 1).

When such a question of safety exists, the Panel concludes that the existence of safer and equally effective products must have weight in the determination of acceptable risk or adequate safety. The prospect of the acceptance of an unnecessary risk in one form of a product when forms that are generally recognized as safe are available, is significant to a consideration of risk-benefit.

E. HISTORICAL DEVELOPMENT

Zirconium compounds were first used as antiperspirants in the 1950's when sodium zirconium lactate was incorporated into a deodorant stick. Soon after introduction of this compound into the American market, users developed small, flesh-colored, indolent papules (small elevations of the skin) in the axillae. Papules would occur in streaks in a configuration which could be explained by a reaction to some material introduced along cuts induced by shaving. Shelley and Hurley (Ref. 2) concisely reviewed the experience of America dermatologists with this new clinical entity (Refs. 3 through 9). Histologically these papules resembled the so-called granuloma seen in sarcoidosis, a disease which can affect many organs of the body and is of unkown cause.

Several years later a different zirconium salt, zirconium oxide, was introduced for use on the skin, this time as a treatment for poison ivy dermatitis. Again, the areas of skin treated with the zirconium oxide cream developed small papules which, when biopsied, revealed epithelioid-cell granulomas (Refs. 10 through 14). It had thus been established that two zirconium products, sodium zirconium lactate and zirconium oxide, could cause sarcoid-like granulomas when introduced into human skin.

Although attempts to produce comparable skin granulomas in animals were unsuccessful, it was possible to reproduce the disease regularly in man. Shelley and Hurley (Ref. 9), and Epstein (Ref. 15) concluded on the basis of their studies that the mechanism responsible for zirconium granulomas in man depended on allergic hypersensitivity. The conclusion that zirconium-induced granulomas were a reaction of allergic hypersensitivity was based on the course of the disease, the time required for elicitation of a positive response, the individual's varied reaction and the minute, microgram dose required to elicit the response. Definitive supportive evidence in the form of sophisticated in vitro immunological techniques was not then available for the study of this process. The absence of a suitable laboratory test animal also limited the amount of investigation which was then possible.

As will be discussed later, while the allergic hypersensitivity mechanism remains a probable one, it is by no means out of the question that other mechanisms now known to account for granuloma formation might also be operative for zirconium-induced granulomas. Because sarcoid-like lung disease may result from the inhalation of many substances, the Panel has been particularly con-

cerned about the safety aspects of zirconium-containing aerosol antiperspirants. In addition to the cases of skin granuloma due to sodium zirconium lactate and zirconium oxide reported above, the Panel considers the following reports of disease induced by these and other zirconium compounds pertinent to this discussion.

F. PUBLISHED SCIENTIFIC REPORTS

1. Epstein (Ref. 15) produced granulomas in three sensitized individuals with several zirconium compounds. These included zirconium carbonate, zirconium oxychloride, mixtures of zirconium oxychloride and glycerine, zirconium lactate and zirconium chlorhydrate. The intact zirconium-aluminum-glycerine complex did not produce skin granulomas in any of these individuals.

2. Obermayer (Ref. 17) reported a case of axillary granuloma. The cause and effect relationship with the woman's deodorant was not conclusively shown. At the time of this report only one zirconium-containing antiperspirant was marketed and it contained zirconium-aluminum-glycine complex.

3. Prior, Cronk, and Ziegler (Ref. 18) exposed rabbits to a mist containing very high concentrations of sodium zirconium lactate daily for 6 weeks. At the end of that time all test animals showed effects in the lungs such as bronchiolar abscesses, lobular type pneumonia or peribronchial granulomas. Prior's work has been criticized on the basis of the very high concentrations of sodium zirconium lactate (49,000 milligrams/cubic meter of air) used in this test. It is possible that a simple overload of the rabbits' respiratory system was responsible for many of the changes seen.

4. The same criticism cannot be levied, however, at the studies of Brown et al. (Ref. 19). Brown and his associates treated groups of 10 guinea pigs, 10 rats, and 10 hamsters for a period of 225 days by inhalation exposure to either 15 or 150 mg/cubic meter of air of zirconium lactate, to 15 mg/cubic meter of air of barium zirconate, or to room air. In the animals exposed to room air, no significant changes were seen. In the animals exposed to zirconium lactate at a concentration of 150 mg/cubic meter of air, the lungs showed more pathological changes. These included pleural thickening, thickening of alveolar walls, and localized deposition of round cells in subpleural areas. Changes in the bronchi and bronchioles were minimal. Of even more interest were changes seen in the animals who were exposed to the lower dose of 15 mg/cubic meter of air. Marked pathological changes similar to those seen in the group receiving the higher dose were observed, but the animals receiving the lower dose had these changes to a much greater degree. In addition to the more severe changes in the animals treated with the lower dose, were findings in the lungs of these animals of a number of giant cells, although no granulomas. Animals treated with barium zirconate at a concentration of 15 mg/cubic meter of air developed comparable pathological changes. These were even more substantial than those produced by zirconium lactate. The general pathological picture in the lungs of these animals was one of a chronic interstitial pneumonitis with associated hypertrophy of the media of the arterioles, which in some cases had led to complete occlusion of the vessels. It was noted that removal of some of the animals from the dust exposure for a period of 3 months did not cause any marked regression in the lung pathology.

Studies attempting to define an immunologic mechanism for production of these pathologic changes were not conducted. The finding of more severe changes in animals exposed to a lower rather than higher dose, however suggests that such might be a possible explanation. Whether immune mechanisms or other factors are involved, the medical experience with pneumoconiosis (a chronic fibrous reaction in the lungs eventually resulting in reduced lung function) includes instances in which people living in the neighborhood of a beryllium processing plant had more severe disease than the beryllium workers themselves (Ref. 20).

Investigators in one submission (Ref. 21) noted that the fact that Brown, et al., amidst all the changes they produced in their experimental animals, did not observe formed granulomas. The Panel's interpretation of Brown et al. was different. The Panel is concerned about the possibility of zirconium-induced serious lung disease which begins with inflammation and goes on to produce fibrosis. The fully formed sarcoid-like granuloma, such as was seen in the skin, may not regularly appear in the lung even under the same sort of stimulus as produced the skin granuloma. Furthermore, the finding of giant cells suggests that comparable mechanisms may be operating because giant cells are characteristically found in granulomatous reactions.

5. An even more significant report was made available to FDA (Ref. 22). In this study, cynomolgus monkeys were exposed to an aerosol of an antiperspirant spray whose active ingredient was a complex of aluminum chlorhydrate and zirconium chlorhydrate. This product's composition was similar to one marketed zirconium-containing aerosol antiperspirant and differed from the other only in the absence of glycine. The test protocol specified the monkeys be exposed to the zirconium-containing aerosol antiperspirant for 15 seconds every 5 minutes for a period of 20 minutes in the morning and again in the afternoon. The test was continued for 90 days. The results in the monkeys' lungs showed "histopathologic pulmonary findings of granulomatous reactions in the terminal bronchioles." The analysis of the changes was of a "terminal bronchiolitis, with an inflammatory response exemplified by increased macrophagic activity."

6. Shelley (Ref. 23) studied the effect of the injections of several metal salts into the external ear of mice. Changes described as cartilaginous dysplasia (cartilage abnormality) were produced by the injections of zirconyl chloride or hafnium oxychloride, but not by a variety of other metal salts including aluminum chloride, beryllium sulfate, cadmium acetate, chromium potassium sulfate, cobalt chloride, and nickel chloride. Shelley concluded that the effects of zirconium and hafnium salts appeared to be unique and predictable. Even though some may consider this work irrelevant to the zirconium-containing aerosol antiperspirant issue, it does show a further toxicity of a zirconium compound.

7. Brackhanova and Shkupko (Ref. 24) found that zirconium hydride given in an intratracheal dose at 15 mg to rats caused pneumoconiosis. The effect was five to six times less severe than that caused by silicon dioxide. Silicon dioxide is recognized as a fibrogenic dust.

8. Mogilevskaja (Ref. 25) found that aerosols which contain metallic zirconium and zirconium dioxide produced a mild fibrogenic (formation of fibrotic tissue) reaction in rats. Inhalation of soluble zirconium salts produced further damages as well as a general toxic reaction. The changes were interpreted as being those suggestive of a tissue response arising from a low grade irritant.

G. THE RELATIONSHIP OF INHALED PARTICLES, LUNG DISEASE, GRANULOMAS AND FIBROSIS

The problem of lung disease caused by inhaled aerosols is a complicated one which has recently received much attention. Parkes (Ref. 26) provided a recent comprehensive review of much of this material. A much more detailed treatment of theoretical aspects of the problem may be found in the symposium on inhaled aerosols edited by Lourenco (Ref. 27). The study of human disease caused by inhaled particles is a dynamic and rapidly moving field. The traditional tools of the epidemiologist and the morphologist are now being augmented by those of immunologists, electron microscopists, physical chemists, and others. For example, Miller et al. (Ref. 28) described a patient with no known exposure to pathogenic dust in whom electron microscopy revealed asbestos in amounts too small to be seen with a light microscope. The same group (Ref. 29) reported a patient with sarcoid-like disease in whom minute amounts of talc were established as the probable cause of disease.

Those papers and comparable ones cited in previous references point clearly to the conclusion that forms of pulmonary disease heretofore considered idiopathic (of unknown causation) must now be studied carefully for possible environmental causes. A review of this literature reveals also the substantial difficulty involved in ascribing causality of a sarcoid-like lung disease to various environmental agents.

In current medical practice a substantial amount of recognized granulomatous disease is of unknown cause. The term sarcoidosis is applied to one group of granulomatous changes whose cause is unknown but in which the clinical course often conforms to a recognizable pattern.

Since its tendency to induce granulomas is crucial to the Panel's concern about zirconium, the Panel will summarize very briefly what is meant by the term granuloma. The granuloma (Ref. 30) is considered to be a distinctive form of inflammatory reaction which results when cells of the mononuclear phagocyte system encounter some substance they are unable to eliminate effectively.

The cells of the mononuclear phagocyte system are scavenger cells, widely dispersed throughout the body. It is now recognized that they are all derived from a common precursor (source) cell in the bone marrow. Depending on where they are located in the body, they take on different appearances and are called

by different names. These locations and names include circulating blood (monocytes), connective tissue (histiocytes), liver (Kupffer cells), lungs (alveolar macrophages), lymph nodes (free and fixed macrophages), bone marrow (macrophages), and serous cavity (pleural and peritoneal macrophages). The osteoclast of bone tissue and the microglial cells of the nervous system are possibly also cells of this type. The term granuloma is used for the lesion produced by those cell aggregates when organized in a particular fashion.

As long as these cells are effectively able to remove foreign substances from their respective tissue, no cell aggregation occurs. It is thought that in at least three instances this effective elimination of foreign substances may be impaired and cells derived from mononuclear phagocytes aggregate.

One such instance occurs when the foreign substance has low biological activity for which there is no effective mechanism of elimination. Here the mononuclear phagocytic cells become stuffed with material that resists the cell's degradative enzyme system. These cells are immobile, resistant, long-lived macrophages which do not divide. These cells store the offending substance, often over a prolonged period. The granuloma thus formed is metabolically relatively inactive and has been termed a "low turnover" granuloma.

A different form of granuloma occurs in two other instances. In one of these, the foreign substance is toxic to the scavenger cell and damages it, releasing further toxic material into the tissue. In the other, the foreign substance acts as an allergen and brings cells of the body's immune system into play. In both of these cases, when the foreign substance is toxic or when it acts as an allergen, the resulting granuloma is characterized by a metabolically active derivative of the mononuclear phagocyte called the epithelioid cell and also by a form called the giant cell. Such granulomas are now termed "high turnover" granulomas.

Unlike the low turnover granulomas in whose cells the offending agent is easily found, the cells of the high turnover granulomas usually do not reveal the presence of the causative agent. The epithelioid cell granuloma has thus been more difficult to study and understand. More recently, however, it has been found that present techniques of immunology have helped to clarify the nature of high turnover granulomas caused by immune mechanisms (Ref. 30).

Of considerable interest is the recent observation that the mononuclear phagocytic cells of the granuloma produce a substance which acts as a stimulant to nearby connective tissue fibroblast cells. These fibroblasts are stimulated to produce more collagen, the basic fiber of connective tissue (Ref. 30). This effect of granuloma cells on fibroblasts would seem to explain the tendency of chronic granulomatous disease of the lung to result in a condition called pulmonary fibrosis. In this condition the required mobility of the breathing process is interfered with by excessive amounts of connective tissue in the lung.

H. THE PANEL STATEMENT OF NOVEMBER 27, 1974

The previous discussion of the nature of granulomas was taken from the Panel's statement of November 27, 1974. That statement was based on the Panel's assessment of the zirconium-containing aerosol antiperspirant problem. It was written following the review of pertinent literature and after a 2-day open session in which a number of invited distinguished experts in the fields of granuloma pathology and pathophysiology and of pneumoconiosis participated. These experts answered the Panel's questions for 2 days. A transcript of that session is available (Ref. 30). All these experts emphasized that further testing was required. At no time during the 2-day open session would any of the experts state that, in their opinion, zirconium-containing aerosol antiperspirants were generally recognized as safe.

Following the open session with the testimony of experts and after a careful review of submissions of zirconium-containing aerosol antiperspirants and their respective ingredients, the Panel issued a statement on November 27, 1974, which expressed concern about the safety of zirconium-containing aerosol antiperspirants. It was the opinion of the Panel that some zirconium-containing particles would be inhaled from the use of these zirconium-containing aerosol antiperspirants, and that there was inadequate information about the fate of inhaled zirconium-containing particles once they reached the lung. The Panel noted a lack of information about how particles were excreted, at what rate, and whether they broke down into products releasing zirconium in forms which might be allergenic or toxic in other ways. The Panel was unconvinced, in view of the brief history of the use of zirconium-containing aerosol antiperspirants, that

long term use in susceptible subjects would not result in development of pulmonary fibrosis. The Panel concluded that tests to measure the immunogenic potential of zirconium-containing aerosol antiperspirants had not been done. The Panel was not satisfied with the follow-up that had been made on users who had complained of respiratory difficulty after exposures to zirconium-containing aerosol antiperspirants. At that time, the Panel discussed the zirconium-containing aerosol antiperspirants in light of what they perceived as benefit-to-risk considerations. It was pointed out that comparable degrees of control of underarm perspiration could be achieved either with zirconium-containing cream products or, in fact, with the most effective forms of aluminum chlorhydrate-containing roll-ons. Although consumers would be expected to want the most active antiperspirants available, it by no means seemed clear that consumers could always perceive the kinds of difference in activity that could be determined in laboratory studies. The majority of users, for instance, preferred aerosol sprays of aluminum chlorhydrate to creams or roll-ons containing the same ingredients, even though the latter were somewhat more effective than the sprays.

Although the Panel had voted at its November meeting to place zirconium-containing aerosol antiperspirants in Category II (not generally recognized as safe) the Panel agreed, when requested by industry, to express its concern and position with a statement and to defer a decision until industry could respond.

I. ASSERTION OF SAFETY FROM REPRESENTATIVES OF INDUSTRY

On December 16 and 17, 1974, representatives of industry presented their reasons for believing that zirconium-containing aerosol antiperspirants did not present a hazard to health. Their case was supported by supplemental submissions (Ref. 31). Because these submissions represent the basis for industry's assertion that zirconium-containing aerosol antiperspirants are safe, the Panel's analysis is set forth in the following sections.

Four main conclusions were offered by industry as follows:

1. Aerosol antiperspirants containing zirconium-aluminum-glycine complex have shown no potential for producing granulomas of the lungs.

2. Zirconium-aluminum-glycine complex is cleared from the lung by the mucociliary escalator (natural lung clearance mechanism whereby hair like projections called cilia transport particles out of the lung) and is eliminated through the gastrointestinal tract.

3. Zirconium-aluminum-glycine complex does not contain zirconium chlorhydrate.

4. Zirconium-aluminum-glycine complex does not break down in the lung.

Particular attention will now be paid to these four points and their supporting data; later comment will be made generally on other portions of these submissions and also on the other supplemental submissions.

1. "Aerosol antiperspirants containing zirconium-aluminum-glycine complex show no potential for producing granulomas of the lungs."

It is the Panel's opinion that this statement, viewed in the most favorable light possible, can only be described as conclusory and not supported by specific data. In the Panel's considered view, published reports of disease induced by several zirconium salts, the testimony of experts about the risks of inhaling zirconium-containing aerosol antiperspirants and some aspects of the submissions themselves are sufficient to justify the contrary conclusion: a real possibility exists that zirconium-aluminum-glycine complex will induce lung disease.

2. "Zirconium-aluminum-glycine complex is cleared from the lung by the mucociliary escalator and eliminated via the gastrointestinal tract."

Three experiments in the submission are adduced to support this assertion. They are as follows:

(i) Each of 2 rabbits was intratracheally infused (Ref. 32) with solutions containing either 0.5, 5.0, or 50 mg of zirconium-aluminum-glycine complex, or 0.073, or 7.3 mg of sodium zirconium lactate (volume of solution not provided). The 2 animals dosed with 50 mg of zirconium-aluminum-glycine complex were sacrificed 5 days after dosing, All other animals were sacrificed 15 days after dosing. Lung tissue was obtained from all animals and was examined by an electron microscope x-ray analyzer for the presence and distribution of zirconium and aluminum.

Ashed samples from some (an undisclosed number) of the rabbits were examined for zirconium. Zirconium was detected only in the group dosed with 7.3 mg of sodium zirconium lactate. The experimenter concluded that, even at an

exaggerated dose of 50 mg, zirconium-aluminum-glycine complex is cleared from the lung within 5 days, whereas sodium zirconium lactate is not cleared even after 15 days. From the submission it is not clear how many rabbits were used in the experiment since either 6 or 12 animals were present at the beginning and only 4 or 8 were reported on at the end. Similarly, the experiment promised data on six different solutions of zirconium-aluminum-glycine complex and sodium zirconium lactate, but present results for only four solutions. The concentrations of the solutions were not given nor was the actual technique of intratracheal infusion used described. It is not clear whether the final ashed samples listed represent pooled or individual samples. This experiment, as described, does not support the conclusion that zirconium-aluminum-glycine complex is cleared from the lung by the mucociliary escalator and eliminated via the intestinal tract.

(ii) In another experiment 75 mg of powdered zirconium-aluminum-glycine complex was intratreacheally infused into 2 rabbits. One animal was sacrificed within a few minutes after dosing; the other after 16 hours. The trachea and lungs were removed and sectioned. The tissue was ashed and analyzed for both zirconium and aluminum by x-ray fluorescence. The results showed that the zirconium-aluminum-glycine complex had been substantially cleared from the lung in 16 hours and that the zirconium-aluminum-glycine complex remaining after 16 hours was in the upper portion of the lung, indicating that the material is being cleared by the mucociliary escalator.

The Panel agrees that properly conducted powder insufflation experiments of the type described are useful. But such experiments can show only how materials presented to the lungs by powder insufflation may be distributed and cleared. Aerosolized particles of respirable size and characteristics can be distributed within the lung in a manner completely different from those introduced by powder insufflation. This is not a minor technical point but a major reason for substantial investments in inhalation toxicology by industrial firms and test laboratories. Particles produced by a propellant system would be expected to have typical characteristics which are quite different from powdered material for insufflation; for example, different particle size and surface characteristics. This, in turn, would influence the amount of material that reaches the lower lung. Propellant generated particles would be more likely to reach the deepest portions of the lung because of their smaller particle size characteristics.

Lung retention studies of insoluble aerosol particles, including zirconium oxide, have shown effective half-lives of 1000 days in the lungs of beagle dogs (Refs. 30 and 33). The major portion of zirconium-aluminum-glycine complex particles are expected to be insoluble. In general, the class of insoluble particulate aerosols are more likely to remain in the lung than relatively soluble aerosols (Ref. 30). The Panel cannot accept conclusions about the safety of zirconium-aluminum-glycine complex aerosol products without definitive measurements of pulmonary retention times as well as the anatomic distribution of zirconium-containing aerosol antiperspirant particles in the respiratory tract.

(iii) The clearance of zirconium-aluminum-glycine complexes from the lung was investigated in another pilot study. According to the submission: "Guinea pigs were intratracheally infused with doses of either 0.8 or 7.7 mg of zirconium as zirconium-aluminum-glycine complex, which are 300,000 to 500,000 times that of human exposure. The material used was radiolabeled with zirconium^{95} [radioactive zirconium]. The absorption, distribution, and elimination of zirconium-aluminum-glycine complex was followed by radioactive analysis of all tissues and excreta."

These experiments are cited to show that when aqueous solutions of zirconium-aluminum-glycine complex are introduced into the lungs of guinea pigs, there is minimal systemic absorption, and that essentially all of the zirconium-aluminum-glycine complex is found in the lung, gastrointestinal tract, and feces. It is claimed further that levels in the gastrointestinal tract and feces indicate that the material is being cleared by the mucociliary escalator.

The Panel agrees that for intratracheally infused solutions of zirconium-aluminum-glycine complex, the results support the assertion that there is minimal systemic absorption. This is not proof of the complete lack of systemic absorption, nor is it proof that absorption, if it occurs, may not produce disease. Since these solutions were intratracheally infused, little can be concluded from the experiment regarding the clearance of aerosolized particles. This experiment is cited to support the general conclusion that zirconium-aluminum-glycine complex is cleared from the lungs by the mucociliary escalator and then from the gastrointestinal tract, but this conclusion is clearly unsupported for aerosolized particles. Furthermore even for intratracheally infused particles, the experimental results ignore

the real possibility of clearance by the general circulatory system via the lymphatics, blood, and bile. Statements that the mucociliary escalator can effectively clear respired particles can be made about almost any respiratory inhalant if the particle size is in a specific range. The well known ability of many inhalants to produce lung disease should be proof that the mucociliary escalator mechanism cannot be relied on for complete protection. Since reliance was placed on the ability of the mucociliary escalator to clear inhaled zirconium-containing aerosol antiperspirants from the lung it must be emphasized further that this mechanism cannot be relied upon to totally remove inhaled particles of zirconium-containing aerosol antiperspirants because of particle size differences and solubility factors.

This problem is discussed in a current reference source (Ref. 26) on inhalation-induced lung disease:

"Both inert and cytotoxic insoluble particles which are deposited in the conducting airways above the terminal bronchioles are eliminated either in a free (that is, extracellular) state or within macrophages via the mucociliary 'escalator' and are expectorated in sputum or swallowed usually about 12 hours after inhalation. However, in the gas exchanging region distal to the terminal bronchioles, the behavior of inert and cytotoxic particles appears to be different.

"Inert particles deposited in alveoli tend to remain in the alveolar area and to be eliminated mainly by the bronchial route. They are engulfed by macrophages which migrate from the alveoli over the nonciliated zone of the respiratory bronchioles to the mucociliary 'escalator' in the terminal bronchioles. It is not understood how they are able to bridge this gap but it has been suggested (Ref. 34) that a proximal movement of surfactant may be responsible. Particles lodged in the interstitium may be carried by macrophages in tissue fluids to the lymphatics whence they travel to intrapulmonary and hilar lymph nodes, but others are retained or 'stored' in the interstitial site for years.

"Smaller insoluble particles tend to travel to hilar lymph nodes more quickly than larger ones, but quartz particles reach the lymphatics more rapidly than non-toxic particles, such as titanium oxide, of similar size (Ref. 34). Furthermore, some small particles may pass into the blood stream; this explains the occasional presence of silicotic lesions in the liver and spleen and other organs.

"The efficiency with which insoluble dusts are removed from the lung varies, therefore, according to whether they are inert or cytotoxic as well as upon the load or concentration of particles imposed upon the elimination routes. Soluble particles dissolve readily and pass into the capillary blood or, possibly, are bound to lung tissue proteins; hence, if they are toxic they may cause damage either systemically or locally.

"The process by which inert and cytotoxic dusts pass from the alveolar lumen into the alveolar wall or its adjacent interstitium is obscure. Breaching of the wall by damage to Type I pneumocytes is thought to occur by some workers (Ref. 35) but is denied by others. There is experimental evidence to show that particles may penetrate into the alveolar wall without the mediations of phagocytic cells (Ref. 36) and that this tends to occur where alveoli are in opposition to bronchiolo-vascular bundles."

The Panel concluded that studies of the hilar regional lymph nodes are essential because they are often involved in sarcoid-like pulmonary disorders. It therefore seems mandatory that examination of these nodes be included in studies of the clearance and distribution of zirconium-containing aerosol antiperspirants.

A much more detailed analysis of the problem of removal of aerosolized products from the lung is given by Morrow (Ref. 37). That article is comprehensive, and contains 130 references; it cannot be summarized briefly but deserves attention in this context.

The Panel has already commented about the technical problems in the experiments designed to show that the mucociliary mechanism can be expected to remove all inhaled particles of zirconium-aluminum-glycine complex. A brief review of Morrow's work and the accompanying paper by Green (Ref. 38) would indicate that such an inclusive statement as "zirconium-aluminum-glycine complex is cleared from the lung by the mucociliary escalator and eliminated via the gastrointestinal tract" cannot be supported in light of the present level of knowledge about how inhaled materials are removed from the lung. The Panel would emphasize again that certainly much of the inhaled zirconium-aluminum complex is removed from the lung by the mucociliary escalator mechanism. But, based on the substantial amount of current information, it is unlikely that all could be removed that way, nor do the studies cited prove it.

This major portion of the claimed basis for safety made to the Panel must be regarded as unsupported by the evidence.

3. The third of these four assertions states: "Zirconium-aluminum-glycine complex does not contain zirconium chlorhydrate." A similar statement appears in another submission (Ref. 22).

In the latter submission, the statement is made that the zirconium-aluminum complex product in question does not contain zirconium chlorhydrate. In each case the Panel will assume that the meaning of the statement is that the final zirconium-containing antiperspirant product is a complex of aluminum and zirconium and no longer contains zirconium chlorhydrate. The implication of this statement is that the zirconium-aluminum-chlorhydrate complex, with or without glycine, thus formed is a unique new entity which will remain intact. The thrust of the statements in OTC Volumes is that zirconium-aluminum-glycine complex is such a product. Evidence cited in another submission states that the zirconium-aluminum complex product described therein is equally as stable as zirconium-aluminum-glycine complex and no more likely to yield zirconium chlorhydrate (Ref. 22).

Submissions state that zirconium-aluminum-glycine complex or zirconium-aluminum complex will not hydrolyze to zirconium chlorhydrate. This is a reasonable concern since zirconium chlorhydrate was found to produce a granuloma when injected by skin test into a patient previously sensitized to zirconium lactate (Ref. 39).

As will be shown, the Panel is uncertain about the nature of the zirconium derivative product(s) which may be derived from zirconium-aluminum-glycine complex or zirconium-aluminum complexes when they are introduced into the body. In a report (Ref. 31), it was shown that when zirconium-aluminum-glycine complex is mixed in vitro with human blood serum "the solubilization of aluminum and zirconium by blood serum appeared to be a real effect." The investigator was unable to characterize these solubilized aluminum and zirconium products further except to indicate that they were of a high molecular weight.

Whether or not zirconium-aluminum-glycine complex "contains" zirconium chlorhydrate seems less to the point than the fact that zirconium-aluminum-glycine complex will release some solubilized zirconium product upon contact with serum.

Since many conclusions have been drawn with reference to zirconium's chemical reactions, further analyses of submissions relative to zirconium chemistry are as follows:

Ultracentrifugation studies on zirconium-aluminum complexes and zirconium-aluminum-glycine complexes show that these complex molecules exist as polymeric species (a high molecular weight compound formed by the combination of simpler molecules). A wide range of polymeric sizes with an average molecular weight of 2000 daltons (defined as a unit of mass, 1.65×10^{-24} gm) was shown to be present in aqueous solutions of zirconium-aluminum-glycine complex under ambient, i.e., normally fluctuating, conditions by use of the analytical ultracentrifuge. As the pH of the zirconium-aluminum-glycine complex solution is increased (decreasing acidity), there is a tendency to increase the amount of higher molecular weight species until, at a pH between 5 and 6 (slightly acidic), the material gels. Though the structure of the insoluble gels has not been established, the experimental evidence reported suggests that it is an extremely high molecular weight polymer. The polymerization process appears to be reversible.

A number of studies were carried out to examine the stability of zirconium-containing aerosols under differing conditions. In the case of zirconium-aluminum-glycine complexes, such investigations were carried out in a number of stressing systems such as phosphate buffer at pH 7 (neutral solution), simulated serum electrolyte at pH 7.4 (slightly basic), macrophage lysate (obtained by exposing rabbit lung macrophage to ultrasonic waves), viable macrophage (concentration determined to be 6 to 7×10^4 cells/ml), hamster lung homogenate and rabbit lung surfactant. The general procedure in these experiments was to incubate the zirconium-aluminum-glycine complex in the particular system and then analyze the supernatant solution of the filtered system for the presence of zirconium and aluminum. The results reported suggest that zirconium-aluminum-glycine complex is not broken down into soluble species of low molecular weight. These studies were not capable of determining any insoluble or high molecular weight zirconium complexes of organic materials in the stressing systems.

The stability of zirconium-aluminum-glycine complex and zirconium-aluminum complex gels in the physiologic pH range (7 to 8) was studied as a function of lactate ion. It was found that when the molar ration of lactate ion to zirconium was increased above 3 (that is, more than 3 lactate ions to every zirconium ion), a substantial degree of solubilization of zirconium and aluminum took place.

When the ratio was below 3, the amount of aluminum and zirconium detected in the supernatant solution (solubilized material) was minute but above zero at the limit of the analytical procedure; that is, 5 parts per million (ppm) for aluminum and 1 ppm for zirconium.

In one series of stability studies on zirconium-aluminum-glycine complexes, the commercial aerosol products were tested. In these studies the aerosolized materials of two commercial products were sprayed into centrifuge tubes and a variety of buffer solutions at pH 7.4 were added. In addition, tests with pooled human blood serum were carried out. The results show that while the hydrolysis of zirconium-aluminum-glycine complexes does not take place in the buffer systems it does take place in blood serum. The approximate order of the solubilization effect in human serum was zirconium-aluminum-glycine complexes, 44 ppm of complex solubilized; a commercial zirconium-aluminum-glycine complex product, 42 ppm of complex solubilized; zirconium chlorhydrate, 37 ppm of complex solubilized; another commercial zirconium-aluminum-glycine product, 10 ppm of complex solubilized. These numbers are the average concentration in ppm of aluminum plus zirconium in these studies. "The solubilization of aluminum and zirconium by blood appeared to be a real effect," the investigator said (Ref. 38). Results of centrifugation of the serum solutions suggest that the majority of the soluble zirconium and aluminum species were of molecular weight greater than 5000 daltons; however, a significant amount of soluble species were below this size. The experimenter who carried out this study pointed out that although the concentration of solubilized aluminum generally exceeded that of zirconium, occasionally the opposite situation occurred. This would suggest nonuniformity in the breakdown by serum of gelled zirconium-aluminum-glycine complexes. This experiment points out the urgency in finding out which materials present in blood enable it to hydrolyze zirconium-aluminum-glycine complexes. Do similar species exist in other organs: for example, the lung?

The aluminum and zirconium in zirconium-aluminum-glycine complexes and zirconium-aluminum complexes will react with alizarin red to form distinctly colored complexes. It is likely that many other organic species will interact with these zirconium-containing antiperspirants to form coordination complexes. It is not inconceivable that some proteins in the body might coordinate with a degraded fraction of a zirconium-containing antiperspirant and become antigenic (Ref. 30).

Charged molecular species will migrate in an electrical field toward either the positive or negative electrode. Cationic species which are positively charged move toward the negatively charged electrode (cathode). Likewise, anionic species are negatively charged and will move toward the positively charged electrode (anode). Aluminum chlorhydrate, zirconium chlorhydrate, zirconium-aluminum-glycine, and zirconium-aluminum complexes are all cationic species while sodium zirconium lactate is anionic.

The electrophoretic mobility, i.e., the characteristic of a molecular species to move toward a particular electrode, is altered by the presence of lactate with the various zirconium-containing antiperspirants. This may be suggestive of some molecular interaction. Only at very high lactate concentrations was some of the zirconium-aluminum-glycine converted to an anionic form.

Another series of experiments was carried out to determine what happens when aerosolized particles of a zirconium-aluminum-glycine complex are deposited on aqueous surfaces which are representative of animal tissue. The results suggest that the buffer capacity of the zirconium-aluminum-glycine complex is sufficient to overcome the buffer capacity of the medium in the immediate vicinity of the particle, thus facilitating its diffusion into the surrounding medium. It is possible that at this diffusional interface, in a biological medium, the zirconium-aluminum-glycine complex might be susceptible to degradation even though the pH of the medium is in the physiological range.

There is clearly a need to investigate the types of interactions that can take place between zirconium-containing antiperspirant and other compounds in tissue proteins.

The Panel was presented with evidence that there may be distinct differences in the toxicological behavior of different zirconium-containing aerosol antiperspirants (Ref. 45). There is thus a definite need to have an analytical procedure which can distinguish between these materials.

The stability of zirconium-containing aerosols was examined in the presence of lung homogenates under conditions in which the tissue was not metabolically active. It is the metabolically active lung tissue that is of major concern to the Panel. Whether or not the viable lung is capable of altering the structure of zirconium-containing aerosols is a question that has not been adequately addressed

in any of the submissions to the Panel. Though zirconium-containing aerosols incubated in the lung homogenates (Refs. 31 and 42) show no solubilization of zirconium-containing aerosol, one must be aware that the metabolically active lung tissue will produce considerable amounts of lactate (Ref. 31). Lactate has been shown to break down zirconium-containing antiperspirants in nonbiological systems (Ref. 31) where the lactate to zirconium ratio is high. That small particles of zirconium-containing antiperspirants reaching the lung experience lactate/zirconium ratios which are high remains to be demonstrated.

4. The fourth assertion in the submission, "Zirconium-aluminum-glycine complex did not break down in the lung," has been touched on already in the previous discussion about zirconium chemistry in paragraph I.3. of this preamble. It was pointed out in that discussion that the critical factor was that when mixed with serum, zirconium-containing glycine complex does solubilize. In this regard, the comments of Morrow (Ref. 37) are pertinent.

In discussing mechanisms of alveolar clearance Morrow says, "However, it has been clearly demonstrated that the terms 'insoluble' or 'soluble' based on *in vitro* measurements (usually in water) are often meaningless in terms of the biological behavior of the substance including its removal from the lung."

The solubiiization of zirconium from zirconium-aluminum-glycine complexes in the presence of serum provides evidence to the contrary. Detailed analysis of the evidence regarding the breakdown of zirconium-aluminum-glycine complex in the lung shows that degradation of zirconium-aluminum-glycine complex does occur in human blood serum after spraying of commercial products into centrifuge tubes containing various buffers. The solubilization of zirconium-aluminum-glycine complex in human blood serum is a real effect, as emphasized by the experimenter himself.

In the opinion of the Panel, that particular study is extremely important because it demonstrates that the zirconium-aluminum-glycine complex is capable of being degraded by body fluids, that is, human serum. This is especially true in light of the fact that any zirconium-aluminum-glycine complex particle reaching the alveoli can readily come in contact with human serum.

Another study was designed to show the effect of hamster lung homogenate on zirconium-aluminum-glycine complex stability. In this study, zirconium-aluminum-glycine complex was incubated with hamster lung homogenates, and subsequently the supernatant of the filtered system was analyzed for the presence of zirconium and aluminum by x-ray emission spectroscopy. The results indicate that zirconium-aluminum-glycine complex is not broken down into soluble species of low molecular weight. The Panel accepts the conclusion from this study. In view of solubilization of zirconium-aluminum-glycine complex by serum, however, the Panel believes that the conclusions cannot be extrapolated to indicate that zirconium-aluminum-glycine complex is stable in an intact lung. For this reason, the importance of using viable, metabolically active lung tissue cannot be overemphasized.

Zirconium-aluminum-glycine complex was incubated with rabbit lung surfactant in another experiment. The Panel agrees with the conclusion that there appears to be no interaction between lipids and zirconium-aluminum-glycine complexes or between lipids and sodium zirconium lactate. The Panel also agrees with the conclusion that the lipid distribution in lipid extracts from rabbit lung is not changed by incubation with either zirconium-aluminum-glycine complexes or sodium zirconium lactate. From this same experiment, it seems that sodium zirconium lactate does not interfere with the lung surfactant lipid either, even though sodium zirconium lactate is known to be biologically active and granulomatogenic. For this reason, the absence of a positive result with zirconium-aluminum-glycine complex is not convincing evidence of biological inactivity.

The Panel concludes that the preceding set of studies performed to show inactivity of zirconium-aluminum glycine complex under physiologically active conditions was not conclusive. Specifically, the Panel pointed out that in the single most representative tissue fluid, serum, the zirconium-aluminum glycine did solubilize, releasing zirconium and aluminum species of high molecular weight. Also, the failure to demonstrate biological reactivity of sodium zirconium lactate in another experiment casts doubt on the conclusion about zirconium-aluminum-glycine complex.

The Panel is impressed with the fact that a series of various buffers of salts did not degrade zirconium-aluminum-glycine complex, but that when serum, a biological fluid, is used, zirconium-aluminum-glycine complex is broken down. Examined in this light, the lengthy submission of December 16 and 17, 1974 is unconvincing because: (i) Statements about the absence of potential for granuloma production appear to be unsubstantiated.

(ii) The claim that zirconium-aluminum-glycine complex is removed by the mucociliary escalator is true to a degree, but it does not suggest the amount that is removed, the other mechanisms involved, or what the rate of removal would be from the lung.

(iii) The fact that zirconium chlorhydrate is or is not a degradation product of zirconium-aluminum-glycine complex is less important than the evidence that small, zirconium-containing products may be released from zirconium-aluminum-glycine complexes.

(iv) The statement that zirconium-aluminum-glycine does not break down in the viable lung is not supported by the evidence in the submission itself and is made unlikely by the fact that zirconium-aluminum-glycine complex is partially solubilized by serum.

J. FURTHER ANALYSIS OF SUBMISSIONS

A close reading of the submission raises further questions about the submitted data.

1. *Inhalation toxicity testing.* Another area in which the data were inadequate concerned the details of inhalation toxicity testing.

A number of subchronic inhalation tests of 90-day duration on various zirconium complexes were conducted using monkeys. Some of these were reported as producing no effects in the lungs of the exposed animals. The data from these studies are summarized in the following table:

TABLE I.—SUMMARY: 90-DAY INHALATION TESTS

Chamber conditions	Number of monkeys per test group	Product tested	Dose dispensed from can into chamber (grams)	Analytical conclusions in chamber, filter weight, milligram per lambert	Histopathologic effects	Exposure conditions
Essentially static	6	ZAR[1]	33	0.034	None	2 30 s bursts per day followed by 15 m retention time in chamber.
Do	8	Vehicle control	33.2	0	do	Do.
Do	6	ZAR[2]	31.6	0.035	Negative in this study, positive in other studies.	Do.
Do	6	ZAR[1]	(*)	0.03	None	Do.
Do	6	Vehicle control	(*)	0	do	Do.
Do	6	ZAR[2]	(*)	0.029	Negative in this study, positive in other studies.	Do.
Do	6	ZAR[1]	35, 39	0.024	None	Do.
Do	6	Vehicle control	38, 29	0	do	Do.
Do	6	ZAG[3]	30.5	0.011	do	Do.
Dynamic	8	ZAR[2]	64.6	0.108	Positive effects	4 15 s bursts, twice a day (a.m., p.m.,) 7 d per week.
Do	8	ZAR[2]	59.7	0.108	do	Do.
Do	8	Control	0	0		Do.
Do	8	ZAG[3]	58.6	0.043	None	Do.
Do	8	ZAR[2]	(*)	0.071	Positive effects	Do.
Do	8	ZAR[2]	(*)	0.052	do	Do.
Do	8	Control		0		Do.
Do	6	ZAG[4]	73.3	0.033	None	Do.
Do	6	ZAG[3]	63.8	0.04	do	Do.
Do	6	Control	0	0		Do.
Essentially static	3	ZAG[3]	[6] 11	(*)	None[5]	3 10 s bursts per day.
Do	3	Control			do.[5]	
Do	3	ZAG[3]	[6] 11	(*)	do.[5]	Do.
Do	3	ZAG[3]	[6] 60	(*)	do.[5]	3 100 s bursts per day.
Do	3	Control	0	0	do.[5]	

[1] Newly marketed zirconium-aluminum complex.
[2] Recalled zirconium-aluminum complex.
[3] Marketed zirconium-aluminum-glycine complex.
[4] New nonmarketed zirconium-aluminum-glycine complex.
[5] High background pulmonary disease.
[6] Approximately.
*Not determined.

One series of tests with zirconium-aluminum complex (0.10 mg/liter) produced adverse effects in monkeys exposed in a dynamic chamber. These effects have been described as mild bronchiolitis. In addition, pre-granulomatous cellular changes were reported. When zirconium-aluminum-glycine complex was tested in the same study, no effects were found. However, the analytic concentration of zirconium-aluminum-glycine complex in this study was less than one-half that of the complex producing the effect. The complex producing the effect was positive at several lower concentration levels (0.071 to 0.052 mg/liter).

In contrast, when another different complex of aluminum and zirconium from a different manufacturer and the zirconium-aluminum complex that produced the adverse effect described above were tested in a simple exposure level at 0.03 mg liter in a chamber with essentially static conditions, no effect was found with either complex.

The results of these studies emphasized that changing the exposure concentrations and the chamber conditions changed the effects attained. Further, these data, taken together, appear to demonstrate a dose-response relationship.

The inhalation tests performed with the marketed zirconium-aluminum-glycine complex products were tested in an essentially static chamber with two exposure levels. Because only three monkeys were used per test group, in contrast to the other tests employing six or eight animals per group, the results should be considered preliminary. No adverse effects were observed in the test animals except for pigment formation from mites in the lungs and subsequent reaction to it. Pneumonitis was observed in the lungs of control and test monkeys. No other lung changes were reported. The high background of pulmonary pathology and the small number of animals make the study inadequate to support safety of the zirconium-aluminum-glycine complex products.

A new, unmarketed zirconium-aluminum-glycine complex was tested for 90 days in a dynamic type chamber at 0.03 to 0.94 mg/liter with a larger group of animals and employed the previously mentioned marketed zirconium-aluminum-glycine complex as a comparative control. In this 90-day study, no adverse effects attributable to either product were observed in the lungs.

Although neither of these zirconium-containing aerosol antiperspirant products that contain zirconium-aluminum-glycine complex produced toxic effects, the Panel does not accept this as adequate proof of safety, considering the intended use of the product. Specifically, this test did not utilize positive comparative controls, did not vary dose levels to establish a dose-response relationship, and was not of sufficient duration. While these studies do not show a toxic effect, they cannot predict the long term hazard that the Panel believes can be found only if long term toxicity testing is done.

The Panel concludes that adequate animal inhalation tests should use an appropriate and adequate number of animals and extend for a longer period of time than 90 days. Also, the animals should be free of complicating background disease to facilitate detection of effects. Dynamic chamber conditions that allow adequate exchange of respiratory gases should be employed, with exposure concentrations chosen to determine a dose-response relationship.

Even though numerous animal inhalation studies have been reported, the lack of a variety of concentrations needed to produce toxic effects in animals was noted in all submissions. The sophistication already available (Ref. 37) in aerosol testing was not reflected in most inhalation studies submitted to the Panel. The Panel would stress careful selection of an animal species for the particular effect being studied. An extrapolation from studies in a single species to man is frequently misleading.

The cynomolgus monkeys have often been used as test animals, and though less prone to lung infestation than the Rhesus monkey, background effects similar to possible effects from zirconium-containing aerosol antiperspirants still make unequivocal conclusions difficult. Since toxic effects with zirconium-containing aerosol antiperspirants have been found in monkeys, this species will likely be one that is selected for study. However, more than one species should be tested.

In some studies, the amount delivered into the chamber was the only parameter known. Because the actual dose inhaled by the animal is dependent on the duration of the spray, the particle size distribution, the breathing rate, the volume of the animal, and the degree of absorption, chamber concentration per se does not sufficiently describe the dose in the animal. Sometimes animals hold their breath and will not breathe for the first few seconds of the burst, adding further complexity to estimation of the dose. The more exactly any of the variables can be controlled, the better. The Panel would agree with most laboratories that do aerosol studies (Refs. 30 and 33) and who recommend dynamic chambers and include accurate dose determination.

In a number of the studies reported, head-only exposure was chosen and the burst was followed by a 15 minute post exposure in the chamber. The Panel would suggest the exposure of the whole body with animals retained in the chamber.

Toxicology testing should include both positive and negative controls to establish the validity of the test. Dose levels should be varied until effect levels are found; once known effect levels are determined, they can be utilized for the estimation of safety factors. Also, only by using dose levels high enough to produce toxic effects is it possible to be sure of all the sites where toxic effects may be seen. Many of these submitted studies did not include an exposure level high enough to produce an effect, and in many cases only one exposure level was utilized. The value of any chronic or subchronic, one-dose study is questionable. Conclusory statements from the test results are meaningless in such cases, especially when an insufficient number of animals, with background disease hard to distinguish from the expected effect, are used.

2. *Granuloma formation.* The Panel would not agree that low-turnover granulomas occur only after extreme overdosing with particulate material, when the mononuclear phagocytic system is presented with particulate material which is neither toxic nor degradable. If the response is a long-lived accumulation of immobilized lymphocytic cells, the reaction, called a low-turnover granuloma by Professor Spector, ensues (Ref. 30). Testimony before the Panel indicates that repeated exposures to insoluble particulate aerosols like zirconium-aluminum-glycine complex are likely to result in the accumulation of these particles in the lung. One cannot dismiss the possibility of granuloma formation based on the assertion that a dose from a single exposure is very small when 30 or 40 years' use of these products can be estimated.

In order to accept industry's proposition that zirconium-aluminum-glycine complex has no potential for producing low-turnover granuloma, the Panel would require data not yet at hand; that is, data demonstrating that, following long periods of use, there is no accumulation of particles in the deep lung.

3. *Safety versus toxicity testing.* The Panel would support the thesis throughout its guidelines that modern toxicologic research dictates that the experiment determine the dose response curve of a material, even if in animal species, so that safety factors can be estimated when normal usage and potential misuse of the product are considered. Studies performed without effect doses in the dosing regimen are not useful for determining a dose response relationship.

This concept contrasts with the older, long held concept of safety testing. In such testing, some multiple of the use level was chosen—normally the use level was used also—and if no toxic effects were observed, the material was considered safe.

4. *Skin irritation and sensitization tests.* The routine tests such as the Draize-Shelanski Test are established and have been routinely run on products to be topically applied (Refs. 50 and 58). The results from a number of these are reported in submissions. The Panel reviewed these procedures and devoted an entire meeting to an extensive discussion with a number of recognized experts (Ref. 40). The experts stated, and the Panel concurs, that for predicting identification of moderate irritants and sensitizers some mechanism for maximizing the test must be developed. In general, the experts and the Panel concluded that the currently used tests would easily pass a moderate sensitizer. Maximization of a test to achieve predictive reliability can be done by irritation of the skin to assure penetration of the antigen, occlusion, increase in induction dose, increase in time of exposure, the addition of biologically active compounds such as Freund's adjuvant to the test material (in animals) or combinations of these. For this reason, the Panel has adopted the position that the submitted tests would not be considered as adequate support of lack of potential for irritancy or sensitization in use.

Zirconium compounds present a special problem in topical testing because of the potential for possible topical granuloma production. One published case (Ref. 12) and numerous consumer complaints describing lumps leave the Panel unconvinced that rare topical granulomas do not occur. Detailed followup of such cases is suggested elsewhere in this document.

A limited number of skin tests in individuals previously sensitized to zirconium have been performed. The number of subjects—three—used in these tests has been understandably low because of the availability of only a small population of potential test individuals who had been previously sensitized to either sodium zirconium lactate or zirconium oxide.

5. *Acute aerosol tests.* (i) Eye irritation tests have been performed with negative results.

(ii) a mouse aerosol irritation test has shown that zirconium-aluminum-glycine complex is a mild to moderate pulmonary irritant by inhalation.

(iii) Acute aerosol tests have been performed repeatedly using a 4-hour exposure with eight 30-second bursts. Some of the tests lacked control groups, and often when controls were used, the animals appeared sick so conclusions were difficult to draw. About the only reasonable conclusion is that guinea pigs or other animals exposed to these dose levels did not die rapidly or in large numbers as a result of the dosing.

It can also be concluded that most animals survived the test conditions; where histologic tests were done and effects were seen, there was confusion caused by high background disease in the control animals.

6. *Sub-chronic aerosol inhalation testing.* The basic aerosol toxicity test has been the one described by Draize, using a 5- or 6-liter static chamber (Ref. 59). More sophisticated techniques of aerosol testing have been developed in the last three decades and better methods are now available.

It should be noted that no aerosol testing whatever was reported for one zirconium-aluminum-glycine complex containing aerosol until a year after it was initially marketed in August 1971. The first aerosol inhalation test with this product reported to the Panel was dated August 1972.

7. *Adequacy of 90-day test period.* The submission of December 16 to 17, 1974, cited a statement by the Society of Toxicology made to the Food and Drug Administration concerning the adequacy of 90-day toxicology studies as determinants of long term effects (Ref. 31). This statement points out that ". . . we believe that the most significant toxicity for drug purposes can be detected at the exaggerated dosages used in toxicological testing from other than microscopic examination of organs. While microscopic examination of tissues is certainly necessary to establish a no-effect dose or safe dose, toxicity is dictated by changes in clinical pathology, body weights, behaviour, or general appearance at the high dose levels." The statement says, "To solidly establish meaningful parameters of safety evaluation usually requires completion of phases I and II in the clinic with appropriate toxicological studies in animals . . . It seems to us that each drug must be evaluated individually, and in the course of the development of the drug that it is the common practice to initiate new animal studies in light of new information." The Panel notes that the Society of Toxicology statement is concerned primarily with the type and adequacy of animal studies run prior to, and concurrent with, phases I and II (human clinical testing) and not with final medical/toxicological clearance of a drug for national introduction. The Panel believes that in light of a specific toxicological potential, those studies required to elucidate that specific problem must be conducted. This is in keeping with experts (Refs. 33 and 42) who, when testifying before the Panel, concluded that lifetime studies might be indicated to determine the potential of these complexes to produce granulomatous or fibrogenic pulmonary disease.

The Panel would not agree that a 90-day subchronic study, even a well-designed and executed one, would necessarily predict the potential for long term granuloma or fibrosis development (Refs. 43, 19 and 33).

The Society of Toxicology statement, as made to the Hearing Clerk in response to proposed FDA guidelines on another matter before the agency, commented primarily on standarized toxicology studies and mentioned some obvious exceptions such as carcinogenicity studies. The Panel believes that an exception would have been made in the Society's statement had animal studies for either hypersensitivity granuloma production or fibrotic lung disease been considered.

Experts testifying about occupational exposure studies involving interstitial fibrotic lung disease stated that it is often decades after exposure that the fibrotic disease surfaces, although some signs may be seen prior to the end of the first decade. As an example, these experts suggested the need to keep exposed dogs longer than 2 years.

An expert witness before the Panel (Ref. 33) indicated that if studies are performed in which animals are exposed for the purpose of determining granuloma or fibrotic response, he considered it necessary to do lifetime studies in the animals. He also recognized that this presents difficulty in clearing products for marketing in reasonable time periods.

Longer term studies were identified as particularly important when consideration is given to a large population that may be at special risk by virtue of already existing impairment of lung function; for example, asthmatics, emphysema patients

or even heavy smokers. The normal animal is virtually always used in inhalation toxicity testing. However, an animal model of proliferative lung disease has been described (Ref. 42). The response of such animals when additionally exposed to zirconium-containing aerosol antiperspirants for long periods of time would provide more pertinent information regarding the possibly increased risk of lung disease to that portion of the consumer population who may be at greater risk.

8. *Particle size determination.* A wide variety of values has been reported for the size distribution of the particles released when zirconium-containing aerosol antiperspirants are sprayed. Values in the submissions range from 50 percent of particles less than 5.5 microns to 6 percent less than 5.5 microns. It is particles in this size range that are of particular concern to the Panel because they are capable of reaching the distal portions of the lung.

Holography and various impaction techniques such as the Anderson Sampler have been utilized. Experts and references in the literature emphasize the importance of an impaction technique for particle sizing when particles are inhaled and deposition is by impaction in the lung (Ref. 44).

It has become evident to the Panel that some portion of aerosol particles produced from use of these products are in the respirable range (below 5.5 microns in size). They are capable of being inhaled and deposited in the alveoli of the deep lung. The panel does not have data on the retention times, mechanism of clearance, or times of clearance for these particles. Because zirconium-containing aerosol antiperspirants produce relatively insoluble particles, evidence in the references just cited indicates that the clearance time may be long, that the amount may increase from daily dosing, and that clearance may result in deposition of particles in the lymph nodes. Time and effort will have to be expended before the details of the required information will be available.

Much research in aerosols has been possible because the conditions of aerosol generation can be well controlled by the use of mono-dispersed aerosols (aerosols generated with uniform particle size). This can be accomplished by examining the ingredient, first in a simple vehicle (mono-dispersed particles) and then in the formulated product (poly-dispersed particles). In this way, the dose, aerosol decay and characteristics of the aerosolized respirable particles can be better understood in both systems.

9. *Cytotoxicity (cell toxicity).* Experiments were reported in several submissions (Ref. 31) designed to show that zirconium—aluminum—glycine complex and zirconium-aluminum complex would be unlikely to act as cytotoxic agents. The Panel's analysis of these data are as follows:

The test of the effects of zirconium-aluminum-glycine complex on lung macrophages in vitro (Ref. 31) was undertaken as a pilot study to provide data on these effects and to compare zirconium-aluminum-glycine complex with two compounds claimed to have detrimental effects on macrophages (Ref. 45). Essentially, the tests consisted of challenging macrophages isolated from the lungs of rabbits with solutions of zirconium-aluminum-glycine complex, sodium zirconium lactate, and beryllium sulfate and then examining the viability and morphology of the treated cells.

It is claimed that the results of this study indicate that zirconium-aluminum-glycine complex does not affect lung macrophage viability or function and that zirconium-aluminum-glycine complex is phagocytized intact and is not degraded by lysosomal enzymes (Ref. 31). These studies are also used to support the more general conclusions stated at the open meeting of the OTC Antiperspirant Panel on December 16, 1974 that "Aerosol antiperspirants containing zirconium-aluminum-glycine complex show no potential for producing granulomas of the lungs" (Ref. 31).

The Panel's comments about these cytotoxicity tests are that, in the submitted data, zirconium-aluminum-glycine complex does not display any qualitative or quantitative difference from sodium zirconium lactate. Sodium zirconium lactate is a known sensitizer and has produced granuloma in human skin and in the lungs of test animals. For this reason it was included as a positive control, assuming that sodium zirconium lactate would reduce the viability of cells exposed to it. Since there was no statistical difference between the results obtained from zirconium-aluminum-glycine complex and those from sodium zirconium lactate, the test must be interpreted as inconclusive.

There was a considerably greater variation in the standard deviation in the data for zirconium-aluminum-glycine complex than in the blank controls. This was pointed out at the open session by one of the invited experts who suggested that such variation could be caused by some experiments in which increased

cell death occurred when cells were exposed to the zirconium-aluminum-glycine complex. No explanation was offered for this wide variation. Several experts invited by the Panel and an industry consultant present at the open session concluded that these cell viability studies are not conclusive about the cytotoxicity of zirconium-aluminum-glycine complex. The Panel concurs in this assessment.

The Panel agrees with the stated conclusions offered with the protein synthesis experiment in which zirconium-aluminum-glycine complex and sodium zirconium lactate appeared to stimulate protein synthesis to varying degrees and where concentrations of beryllium sulfate greater than 10 mg/ml appeared to induce a toxic effect. However, the Panel does not agree that one can draw the conclusion that both zirconium-aluminum-glycine complex and sodium zirconium lactate are inert. These experiments are inadequate, and support no conclusions about the cytotoxicity of zirconium-aluminum-glycine complex or sodium zirconium lactate except, possibly, that these two compounds are less cytotoxic than beryllium sulfate.

Furthermore, study of intracellular protein synthesis within the macrophages exposed to zirconium-aluminum-glycine complex and sodium zirconium lactate showed increased protein synthesis. Although in these tests sodium zirconium lactate at high concentrations showed some indications of inducing focal hyperplasia, zirconium-aluminum-glycine complex and zirconium aluminum complex did not. An increase of lysosomal enzymes in the supernatant fluid or of degranulation within the cell was not looked for. Without such studies, it cannot be logically stated that the ingested particles were not under active attack by intracellular mechanisms.

The Panel agrees that both zirconium-aluminum-glycine complex and sodium zirconium lactate-treated cells appeared normal at the ultrastructural level in comparison with the macrophages exposed to beryllium sulfate. However, the Panel concludes that this is all that the test indicates. This assessment was also offered at the open meeting on December 16, 1974, by experts. Since sodium zirconium lactate is known to produce granulomas in human skin and in the lungs of experimental animals, the Panel concludes that this test is inappropriate and inconclusive with respect to assessing zirconium-aluminum-glycine complex proclivity toward granuloma formation.

The Panel agrees that the x-ray microprobe analyses of zirconium-aluminum-glycine complex exposed macrophages showed that the elemental zirconium and aluminum ratio of zirconium-aluminum-glycine complex was maintained after the particles had been phagocytized by the macrophage. The zirconium and aluminium ratio determined from these analyses is consistent with that in the zirconium-aluminum-glycine complex, but can also be consistent with any number of smaller molecular weight decomposition products of zirconium-aluminum-glycine complex. Therefore, the Panel does not agree that this experiment proves that some zirconium-aluminum-glycine complex had not been chemically altered within the cell. This demonstrates a point made several times in open sessions, namely, that a definitive analytical technique for finger-printing zirconium-aluminum-glycine complex is essential.

10. *Intratracheal infusion of zirconium-aluminum-glycine solution in hamster lungs.* Histopathological examination of the lungs of hamsters intratrachcally infused with three concentrations of zirconium-aluminum-glycine complex was performed. The submitter explained that the results were preliminary but that the only effects noted were characteristic of nonspecific irritation (Ref. 31).

The investigator reports that 24 hours after the first dose (0.2 ml of 0.4-percent zirconium-aluminum-glycine solution) hemorrhaging and edema were evident. One to 2 days after the second inoculation, congestion, hemorrhaging, edema, and macrophage proliferation were histologically observable. The Panel believes that these data do not support conclusions that zirconium-aluminum-glycine complex is inert. Appropriate controls for evaluating possible histological changes indicative of pregranulomatous lesions were not included. The Panel would be interested in learning how this inflammation would compare with that produced by sodium zirconium lactate on the one hand and aluminum chlorhydrate on the other. Without such comparative controls the Panel believes that the information from this experiment does not provide adequate evidence about the question of whether zirconium-aluminum-glycine complex is incapable of producing granulomatous lesions.

11. *Antigenicity/hypersensitivity.* Preliminary attempts were made (Ref. 31) to produce delayed skin hypersensitivity in albino guinea pigs by single injections of complete Freund's adjuvant and either beryllium sulfate, sodium zirconium lactate or zirconium-aluminum-glycine complex. The results were that neither

zirconium-aluminum-glycine complex nor sodium zirconium lactate produced a positive skin reaction but that beryllium sulfate did produce delayed skin hypersensitization in six of nine animals. These data are cited as evidence that zirconium-aluminum-glycine complex has no granulomatogenic potential.

The Panel disagrees. Since in this system sodium zirconium lactate, a known skin sensitizer, did not produce sensitization, the Panel must conclude that the test system was inadequate to reveal the sensitizing potential of suspect zirconium-containing compounds.

Expert testimony at an open meeting (Ref. 33) pointed out that "singleshot" attempts at induction of hypersensitivity are often inadequate. Repeated exposures were recommended instead. It was also suspected by these experts that the 10- to 17-day induction periods allowed in these experiments were possibly too few or too short to induce sensitization. The Panel concurs with these comments. Even with a potent sensitizer like beryllium sulfate, sensitization reqiured a series of 12 biweekly injections (Refs. 46 and 43).

In vitro macrophage inhibition factor tests were performed using sensitized, isolated guinea pig peritoneal macrophages (Ref. 31). The presented data are described as preliminary, and it is stated that no conclusions can be drawn. Nonetheless, this data is cited as evidence for the general conclusion that zirconium-aluminum-glycine complex is not antigenic.

The percent of inhibition in the controls is significant, raising serious doubt as to the validity of these observations. The goal of such a study should be to test for potential sensitization in humans. Blood lymphocytes from zirconium sensitized patients could serve in a test of this kind. It also would be important to find out how zirconium-aluminum-glycine complex previously incubated in human blood and other biologic fluids performed in these tests.

The Panel agrees that these data are preliminary and believes that it is inappropriate to draw any conclusions at this time. Further, the Panel concludes that these data cannot be used to support any conclusion asserting the non-antigenicity of zirconium-aluminum-glycine complex.

The necessity of showing that zirconium-containing aerosol antiperspirants are not antigenic is crucial in any attempt to establish their safety. This is especially important in the light of recent studies which suggest that mucosal surfaces provide a uniquely active site for the development of immunologic hypersensitivity (Ref. 60). The Panel can only conclude that not enough attention has been concentrated on problems of antigenicity and hypersensitivity. In fact, the studies submitted do not seem to be designed to discover the potential antigenicity of the test materials. Rather, the studies seem representative of the safety testing discussed earlier in this document and, therefore, are not consistent with toxicologic evaluation. The Panel cannot agree with the stated or implied conclusions that zirconium-aluminum-glycine complex or zirconium-aluminum complex have been proven to have no potential antigenicity.

12. *Acute inhalation studies in guinea pigs.* In one submission (Ref. 31), the results of acute inhalation studies are cited as evidence to support an assertion that zirconium-aluminum-glycine complex has no potential for the production of low-turnover granuloma.

The dose administered in these acute inhalation studies in guinea pigs was achieved by 8- to 30-second bursts over a 4-hour period followed by a 14-day observation period.

The Panel seriously questions an attempt to test for histologic evidence of granuloma formation 14 days after a single high dose. The Panel believes that this is clearly too short a period to find evidence of fibrotic response. Reeves and Krivanek (Ref. 43) took 16 months to produce evidence of fibrosis in inhalation studies in guinea pigs.

Acute inhalation studies are not the kind of studies to use as a model for animal studies to detect formation of low- or high-turnover granulomas. Many of the experts consulted stated that in developing or studying granuloma models they would not rely on this type of study to predict the potential of a compound to produce low-turnover granuloma because this disease is chronic in nature and develops slowly. Thus, the conclusion that the results of these studies provide evidence to show that zirconium-aluminum-glycine complex has no potential to produce low-turnover granulomas is unwarranted.

13. *Complaint file examinations.* A further source of concern to the Panel came from examination of complaint files voluntarily submitted to FDA (Ref. 47).

On October 1, 1973, one manufacturer voluntarily recalled a zirconium-containing aerosol antiperspirant containing zirconium chlorhydrate and aluminum

chlorhydrate after the product produced a mild bronchiolitis in monkeys in an aerosol inhalation test. In a meeting called with another manufacturer to discuss their zirconium-containing aerosol antiperspirant formulation containing zirconium-aluminum-glycine complex, FDA asked them to submit their complete complaint file to FDA. This file showed 249 complaints received by the manufacturer of that aerosol antiperspirant from the introduction of the product in June 1973 until October 1973.

When this file was reviewed by the FDA physicians, they recommended follow-up on specific cases. The follow-up was to include interviews of patient and physician by FDA inspectors. The inspectors visited these persons and verified the details of the complaints. The decision was made at that time in FDA that it would be impossible to evaluate these complaints unless more complete baseline data on comparable complaint data with aerosolized aluminum sprays were available. Such information was requested, but not enough was received by FDA to draw a conclusion. At that time, FDA personnel turned their files over to the Panel for evaluation.

At the same time, FDA also requested complaint information from manufacturers of aluminum-containing aerosol, cream, roll-on and various other formulations. Although the number of complaints was not as high as is optimal for a baseline, some conclusions as to the type and relative frequency of complaints can be made for nonzirconium-containing aerosol antiperspirants and for non-aerosolized antiperspirants.

FDA again requested the complaint files from the producer of zirconium-aluminum-glycine complex for their zirconium-aluminum-glycine-complex-containing formulation covering the period from October 1, 1973 to November 13, 1974. At this time, FDA also requested all of the complaint files on second zirconium-aluminum-glycine complex formulation marketed by the same zirconium-aluminum-glycine complex manufacturer from its introduction nationally in August 1971 to the present. All of these were submitted to FDA and to the Panel; 406 complaints were received on the first product and 213 complaints on the latter.

These complaint files have been read by Panel members. They asked for additional follow-up material on specific cases. This was provided in a further voluntary submission to FDA. One submitter of complaint files has suggested to the Panel that every product category has a baseline rate of adverse reactions as well as specific types of reactions. It was further suggested that zirconium-containing aerosol antiperspirant complaint data be examined in the light of up-to-date information on adverse reaction complaints for the complete antiperspirant category. Attempts have been made by FDA to collect these data but only a small amount of such data were submitted.

Panel members have analyzed the complaint data. The number of complaints involving coughing, choking or respiratory distress recorded for two marketed zirconium-containing aerosol antiperspirants constituted 13 and 18 percent of all complaints received. The baseline data compiled for aluminum-containing aerosol antiperspirants showed 0.4 percent (1/245) in the period 1972 to 1973. In this same period, another product recorded 5 percent (3/55) choking symptoms.

Based on these admittedly limited data, the Panel concluded that there were significantly more complaints of respiratory distress with zirconium-containing aerosol antiperspirants than with other aerosol antiperspirants.

One of the claims stressed most to support the safety of presently marketed zirconium-containing aerosol antiperspirants is that they have a proven record of safety after widespread use. The Panel would conclude that this claim can be supported only with stringent follow-up of consumer complaints.

Most of the complaint reports were terminated with a physician's recommendation that no follow-up was indicated. From the Panel's reading of these reports, it is not clear if the physicians who reviewed these cases and recommended no further follow-up were the consumer's own physicians or physicians in the employ of the supplier of the zirconium-containing aerosol antiperspirant product. It is assumed they were the latter.

If there is a positive correlation between the use of zirconium-containing aerosol antiperspirants and initiation or exacerbation of specific lung pathology, it can be found only with precise, thorough and complete retrospective examinations of adverse reaction complaints of respiratory distress. Based on this limited follow-up, the Panel cannot accept as proof of safety, claims about the innocuousness of marketed zirconium-containing aerosol antiperspirants.

The Panel recognizes that the protocol for follow-up found in the complaints submitted to them was based on a standard for consumer complaints use. for

cosmetic products. However, the Panel does not consider this type of follow-up adequate to support assessment of hazard in the consideration of general recognition of safety for over-the-counter drug use.

K. DIFFERENCES AMONG ZIRCONIUM-CONTAINING AEROSOL ANTIPERSPIRANTS

A further complication that faced the Panel as it tried to weigh the relative risks associated with the use of zirconium-containing aerosol antiperspirants had to do with the question of how different one zirconium-containing aerosol antiperspirant was from another. The data submitted about zirconium-aluminum-glycine complex repeatedly stressed the uniqueness of zirconium-aluminum-glycine complex as if to separate it from all other zirconium-containing aerosol antiperspirants. On the other hand, the zirconium-aluminum complex submission suggested that in no way could the zirconium-aluminum complex product be shown to be less safe. The possibility that all zirconium-containing aerosol antiperspirants might be safe was contradicted by the experience with a product that had caused disease in monkeys (Ref. 23). The Panel was then faced with the fact that at least one zirconium-containing aerosol antiperspirant was not safe; it had to decide if all other zirconium-containing aerosol antiperspirants or just one other zirconium-containing aerosol antiperspirant was safe.

Because of the difficulty in characterizing the various zirconium antiperspirant products and because the nature of the OTC review process is to write a monograph about ingredients that can be formulated into products, the Panel concluded that the OTC monograph route was not the proper way to insure safety of zirconium-containing aerosol antiperspirants. A better procedure appeared to be the investigational new drug/new drug application (IND/NDA) route in which the manufacturer of a product is able to test his own product in its finished formulation and, based on the results of those tests, apply to FDA for permission to market. In that way, even if some zirconium-containing aerosol antiperspirants were not safe, if a manufacturer could, in fact, provide data to convince FDA that his particular product was safe, he could receive permission to market.

L. MEETING OF JANUARY 31, 1975

Following this analysis of the industry submission, the Panel voted, on January 31, 1975, to categorize zirconium-containing aerosol antiperspirants in Category II on the basis that they could not be generally recognized as safe (Ref. 48). At the same time, the Panel stated that it believed that the major risks associated with zirconium-containing aerosol antiperspirants would be primarily those of long term use. The Panel did not suggest a product recall but did state, "The continued marketing of these products should be contingent upon the vigorous pursuit of safety testing by industry. The Panel plans to provide guidelines for those tests it considered essential."

M. ATTEMPT TO DEFINE GUIDELINES

At its meeting on March 24 to 25, 1975, the Panel set out to define those guidelines which it thought, if followed by industry, might allow continued marketing of zirconium-containing aerosol antiperspirants without subjecting the large numbers of users of these products to an unwarranted risk. At that time, the Panel realized that it was the assessment of industry that the preliminary categorization of zirconium-containing aerosol antiperspirants into Category II by an FDA advisory panel would not only allow companies already marketing zirconium-containing aerosol antiperspirants to continue to do so for some months or years until the administrative process was complete, but would also not deter other manufacturers from bringing zirconium-containing aerosol antiperspirants to market. The implications of this situation were that an even larger number of users would be subjected to whatever were the potential risks of exposure to zirconium-containing aerosol antiperspirants. Nevertheless, the Panel proceeded to try to work out what it thought would be the kind of testing that would be reassuring.

The Panel developed guidelines for zirconium-containing aerosol antiperspirants. The tests are outlined in five parts, consisting of single contact exposure, sensitization, chronic health effects, special studies and human studies:

1. *Single contact exposure studies.* These studies should be designed to determine the acute toxicity of the formulation by various routes of administration and

define dose response relationships. The dosage should be administered by the oral, skin, and intraperitoneal routes. In terms of the inhalation route, the concentration necessary to produce toxic symptoms in the animal within a day should be established. If necessary, the option to increase the number or duration of exposure in the acute inhalation study should be considered. Irritation studies of the eye, mucous membranes and skin should be carried out with the formulation. In these acute toxicity studies, as in all other studies in animals, it is difficult to select a single animal model which would be most appropriate. The Panel stresses that no matter which animals are selected for the proposed studies, comparative controls must be run simultaneously. These would include both positive and negative control materials.

2. *Sensitization tests.* Tests should be run in animals to predict the capacity of a formulation to produce delayed hypersensitivity in man. Among the approaches pursued for these purposes are:

(i) *Animal tests.* Guinea pig maximization test (Ref. 49).

(ii) *Human tests.* When moving from allergenicity testing in animals to humans, the reliability of the Draize test is improved if the concentration of the allergen is increased (Refs. 50 and 51). The 21-day repeated patch test or an adaptation of the Kligman maximization test (Ref. 52), in which the concentration of sodium lauryl sulfate is reduced, were suggested by a group of experts with whom the Panel met in September 1974 (Ref. 40). These experts expressed the opinion that the formulation be tested in addition to the ingredients comprising it.

(iii) *In vitro tests.*

a. Lymphocyte transformation (Ref. 45).

b. Macrophage migration inhibition (Ref. 53).

c. Serum antibody measurements.

3. *Chronic health effects.* Studies of the products should be of sufficient duration to obtain dose response information so that safety factors for any aerosol product can be calculated. These tests should be designed to determine potential toxicological effects both at the site of intended application (skin) and in the respiratory system. The Panel suggests that the repeated skin contact studies should be a minimum of 90 days' duration. The dosages should be applied to both the abraded and unabraded skin of the test animals. The range of dosages should cover the normal use level and include two higher concentrations, and if possible, one which produces a toxicological effect.

The measurements which the Panel feels are important so that safety of the test material can be assessed are as follows:

(i) Percutaneous absorption.

(ii) Distribution, metabolism, and excretion.

(iii) Appropriate function studies conducted serially, to measure physiological changes.

(iv) Hematology and urine analysis to check biochemical functions.

(v) Complete histopathological examination, including organ weights, gross observation, and histology.

A reasonable animal for such a study would be the rabbit. However, other animals such as the guinea pig could be used. Comparative controls should also be employed.

Aerosolized particles produced by propellant systems will usually contain a significant fraction of respirable particles. It is thus exceedingly important to assess the safety factors regarding inhalation of these products over long periods of time.

The major factors that must be considered in developing an inhalation protocol are the mechanics of the inhalation test system, the pulmonary anatomy and physiology of the test animal, and the expected toxicity of the material. There are a number of test systems presently being utilized (Refs. 54 and 55). There are two basic aerosol chamber designs: the dynamic and static chamber systems. The animals in a static chamber system are exposed to the test aerosol in a closed environment; animals breathe only air present in the chamber. The dynamic chamber system permits the aerosol particles to be continuously swept through the chamber at a constant rate. The dynamic chamber makes experimental control of aerosol concentration more reliable. In testimony before the Panel (Ref. 33), Dr. Robert Jones, an expert in aerosol testing, stated that a dynamic chamber is preferable in toxicological studies. A description of the type of inhalation testing chambers is the subject of an FDA report (Ref. 56).

The question arises whether the whole body or just the head of the animal should be exposed to the aerosol particles in tests. Whole body exposure of the

animal would more closely approximate the types of contact usually associated with aerosol products. It is thus the more logical way to carry out the repeated inhalation studies.

The choice of an animal species to be used for the chronic inhalation studies depends on the types of information desired. For example, 90-day inhalation studies with a zirconium-containing antiperspirant formulation using rabbits and rats showed no evidence of granuloma formation in the lung, but cynomolgus monkeys give positive results (Ref. 23). Beagle dogs appear to be good models to measure retention times (Ref. 33). Mongrel dogs have been suggested as good models for comparative studies of respiratory and systemic immunologic reaction (Ref. 57).

Prior to initiation of the long term inhalation testing, a dose-ranging study of approximately 30 days should be carried out to estimate the effect concentration to be used in the chronic study.

The length of study should reflect the duration of exposure of the aerosol product when used by the public. It is the Panel's opinion that these studies should expose the animals for a minimum of 6 months. Some animals in the test series should be held for 3 months following their exposure period. Longer test periods may be necessary in instances where the material is suspected of being granulomatogenic or fibrogenic. A study of the effect of beryllium sulfate on animal lungs took 16 months to produce such effects (Ref. 43).

The exposure levels of the test material should range from a high concentration dose level to the normal use level of the product. Three concentration levels are recommended with at least the highest level producing a toxicological effect. Along with the test product, two comparative controls should be used: a negative control and a positive control.

The Panel suggests the following comparative controls for possible use in these studies,

(i) Aluminum chlorhydrate.
(ii) Sodium zirconium lactate.
(iii) Beryllium sulfate.
(iv) Zirconium oxide.
(v) Commercially available products.
(vi) A zirconium-aluminum-glycine complex or zirconium-aluminum complex.

A number of measurements to gauge any alteration in the normal biochemistry and physiology of the test animals is important. Therefore, hematological tests, urine analysis, appropriate pulmonary function tests, pathology and slit lamp examination of the eyes should be carried out serially on the animals.

The metabolism, distribution and excretion of the test materials should be an integral part of these studies. It may be appropriate to use radiological test materials for such studies.

Information about the pathology produced by the test materials should be obtained from serial sacrifice of the animals and examination of their organs (gross and microscopic examination). The amount of test material present in the lung should be determined to detect any increasing burden to the lung during prolonged inhalation of the product.

4. *Special studies.* A series of special studies is felt to be warranted in the case of aerosol materials that will be used for prolonged periods. These are:

(i) Animal tests for granuloma formation (in vivo).
(ii) Pilot inhalation study to evaluate alveolar macrophage responses.
(iii) A study with rats to evaluate effects on reproduction pathology of exposed rats. Study should be carried out for 2 or 3 generations of the animals.
(iv) Microbiological tests to examine whether microorganisms on the skin surface or in the respiratory tract can alter the chemical nature of the antiperspirant materials.
(v) Experiments in exposed animals to detect any potential of the antiperspirant ingredients to produce teratogenesis, mutagenesis, and carcinogenesis.
(vi) In vitro studies with lung tissue to learn if the antiperspirant materials can be chemically altered or if the zirconium-containing aerosol antiperspirants alter the biochemical or physiologic activities of the lung.

5. *Studies in human subjects.* A series of studies in human subjects should take place only after the previous animal tests have shown that the test product has a large margin of safety. These human studies should consist of skin irritation/sensitization tests and metabolism studies which measure the distribution of active ingredients in blood, urine, and feces. If previous experiments lead to a suspicion that there may be pulmonary effects, pulmonary function tests should be carried

out, and bronchial lavage should be performed to remove macrophages which might be tested for the presence of zirconium compounds.

When test marketing of the product is initiated, close surveillance is required to collect any adverse reactions that may occur. Questionnaires should be circulated to the public to learn the incidence of adverse effects. There should be complete medical follow-ups on all complaints resulting from product use. This would be especially important when complaints are suggestive of pulmonary involvement.

The Panel believes that an adequate evaluation of such subjects should include, although not be limited to, a chest X-ray and pulmonary function tests that would reveal impaired gas exchange or early fibrosis. An appropriate battery of tests would include, but not be limited to:

(i) Tests of volumes and capacity.
   a. Forced vital capacity (FVC).
   b. Forced expiratory volume, 1 second (FEV).
   c. Mid-maximal expiratory flow (MMEF).
(ii) Peak flow.
(iii) Diffusion of carbon monoxide.
(iv) Blood gases.

Where feasible, tests should also include these more sensitive techniques:

(v) Flow volume loops.
(vi) Closing volumes.

Where there is a question of the early changes of fibrosis, it would be desirable to utilize plethysmographic techniques for:

(vii) Frequency dependent compliance or resistance.

Also, the patient's white blood cells should be challenged in vitro with suitable zirconium-containing antigens to reveal the possibility of zirconium hypersensitivity. Skin testing with appropriate zirconium compounds should be performed on patients presenting respiratory or skin complaints.

Should any one of these tests or an especially clear history of association of signs or symptoms with exposure to zirconium-containing aerosol antiperspirants be positive, the Panel would then recommend that the patient be examined by a specialist in chest diseases and that fibre-optic bronchoscopy should be performed to examine the smaller bronchioles for suggestive signs of early granulomatous changes. Pulmonary macrophages should be obtained for further testing against possible zirconium antigens.

Because of the importance of finding out if zirconium-containing aerosol antiperspirants actually could cause human lung disease and because of the hope of finding such cases while still early and reversible, the tests, while difficult, did not seem unreasonable.

After outlining this test protocol, there was a lengthy discussion questioning whether, if tests of this magnitude and duration are required, the Panel had the right to subject a large segment of the American public to these agents that had already been determined by the Panel as not generally recognized as safe.

At this point, the Panel paused to review what had been outlined as a basis for those tests which might serve to provide reasonable evidence about the safety of zirconium-containing aerosol antiperspirants.

N. IMPLICATION OF THE PROPOSED GUIDELINES

First, it had become apparent that the Panel would not be satisfied with negative animal test results on zirconium-containing aerosol antiperspirant products unless many of those tests had been run also with sodium zirconium lactate, zirconium chlorhydrate, aluminum chlorhydrate, zirconium oxide, and aluminum-containing aerosol antiperspirants as comparative controls and, furthermore, unless various time dose factors had been used to produce measurable drug effects for at least some of the agents tested. Unless this were done, as has been pointed out in the preceding discussion of previous submissions (Refs. 31 and 22), it would be impossible to know if the test system employed were capable of showing toxic potential of the compound.

Unfortunately, most of these tests have not yet been done in the described manner. In practical terms, it may well take a period of some months before the precise methodology for these tests is worked out. Also, many of the animal tests would take a long time. Brown et al. (Ref. 19) took 225 days to produce disease in animals; Reeves and Krivanek (Ref. 43) took 16 months with a beryllium salt to produce fibrosis, and beryllium compounds are well known to be highly

dangerous in human beings. When one adds a substantial amount of development time, some of the other 1- and 2-year tests the Panel outlined, and then adds to that the time required to analyze test results, it becomes apparent that a substantial part of the evidence required could not, even under the best circumstances, be available until after a prolonged period.

Were the marketing of zirconium-containing aerosol antiperspirants to be allowed while testing progressed, as suggested by the Panel on January 30 and 31, 1975, it is apparent that many millions of consumers would experience a prolonged exposure to products already characterized as not generally recognized as safe. Should some of the proposed tests reveal a tendency of zirconium-containing aerosol antiperspirants to produce disease, a great many consumers would have unnecessarily been exposed to the risk of developing lung disease.

The second major implication of the proposed testing guidelines concerned the kinds of human studies the Panel had agreed it would need to provide evidence about the safety of zirconium-containing aerosol antiperspirants. The kind of damage zirconium-containing aerosol antiperspirants might produce in human beings is likely to be insidious and hard to detect. The Panel was agreed that there would be no question about advising the Commissioner to order the immediate cessation of sale of these agents if it could be demonstrated that they had, in fact, produced a case of disease. The question was, however, what would constitute a case. Not fibrosis; fibrosis takes years to develop and could not be expected to be seen so soon after the introduction of zirconium-containing aerosol antiperspirants. The early changes induced by zirconium-containing aerosol antiperspirants, were there any, would be hard to find. Certainly they could not be found unless they were sought. The Panel perceived that they would have to be looked for in three ways:

(i) In users who had complained about symptoms.

(ii) In human volunteers with appropriate informed consent who agree to expose themselves to exaggerated doses of zirconium-containing aerosol antiperspirants so that tests of marcophage function, pulmonary function and hypersensitivity could be conducted.

(iii) By means of an epidemiological investigation of the antiperspirant use patterns of various patients appearing in clinics with complaints akin to sarcoidosis and/or pulmonary fibrosis.

This kind of testing would require a major effort, not only by industry but also by large groups of physicians and scientists.

The Panel recognized that the kind of work-up outlined was far more than is ordinarily followed upon receipt of a consumer complaint by industry. It would not, however, seem excessive for a complaint by a patient in a Phase II trial of an investigational new drug.

At the same time, the Panel recognized that investigational new drugs in Phase II or III trials are not dispensed freely, even among patients under careful medical supervision. Such drugs are not used unless the patient's rights are fully protected and monitored by a patient's rights committee, and there is a provision in most cases for written, informed consent.

It was this realization that continued marketing of zirconium-containing aerosol antiperspirants would constitute, in effect, a very prolonged clinical trial without the informed consent of the test subjects that then brought the Panel to consider asking the Commissioner to take steps to have zirconium-containing aerosol antiperspirants withdrawn from interstate commerce until they had been granted approval of an NDA.

Q. REVIEW OF THE PROBLEM

In the discussion of that question, the elements of benefit risk were once again raised. The Panel has deemed several factors essential in its analysis of this judgment.

Certain zirconium compounds have caused human skin granulomas and toxic effects in the lungs and other organs of experimental animals.

Zirconium-containing complexes are the active agents in some aerosol antiperspirants now being sold and in others being readied for marketing.

When used in aerosol form, some zirconium will reach the deep portions of the lungs of users of these products.

The lung is an organ, like skin, subject to the development of granulomas.

Unlike the skin, the lung will not reveal the presence of granulomatous changes until they have become advanced and, in some cases, perhaps permanent.

The Panel was unable to find adequate evidence to support assurances that zirconium-containing aerosol antiperspirants would not produce hidden lung disease in some subjects.

Such evidence will be difficult to obtain and, in any case, cannot be available quickly.

Earlier in this report the Panel has given its analysis of the risk-benefit considerations involved in nonaerosolized zirconium-containing antiperspirants. The conclusion there was that these nonaerosolized antiperspirants are reasonably safe.

A similar analysis of zirconium-containing aerosol antiperspirants leads to a different conclusion. The two kinds of zirconium-containing products are compared point by point, as follows:

1. *Adverse reactions.* The possible adverse reactions (lung granuloma and ensuing pulmonary fibrosis) would be severe and probably not reversible. A lump or rash in the underarm is minor compared with a progressive, worsening lung disease.

2. *Site of injury.* Unlike that of the topically applied zirconium-aluminum-glycine complex antiperspirant, the adverse effect of zirconium-containing aerosol antiperspirant can be expected to occur both in the underarm area and in the lung. The Panel contends that the consumer cannot be expected to anticipate this latter adverse effect. He cannot be warned to discontinue the use of the product or see his physician when lung granuloma develops. He is unaware of any ill effect until it is possibly too late to repair the damage. Lung granuloma disease is an unnecessary risk to assume in the use of zirconium-containing antiperspirants; it is not inherent in their effective use; on the contrary, it is an unnecessary risk associated with the aerosol method of application.

3. *Incidence.* The incidence of adverse reactions using zirconium-containing aerosol antiperspirants are classified as follows:

(i) *Underarm.* The incidence of allergic or non-allergic contact dermatitis and irritation reactions are extremely low, similar to reaction to the nonaerosolized zirconium-containing aerosol antiperspirant.

(ii) *Bronchial.* The incidence of bronchial distress is low. However, from complaint files it appears that bronchial distress is greater for zirconium-containing aerosol antiperspirants than for nonzirconium-containing aerosolized antiperspirant sprays. There are no complaints of bronchial distress from the use of cream or roll-on antiperspirant drug products, including those containing zirconium-aluminum-glycine complex.

(iii) *Deep lung.* The incidence of lung granuloma in users of zirconium-containing aerosol antiperspirants is unknown, but it may well be low. If zirconium-containing aerosol antiperspirants are permitted to be marketed, an annual sale of well over 100 million units can be expected. Even a very low incidence of disease could result in a substantial number of cases of granulatomous lung disease annually in the population at risk.

4. *Body burden.* Because zirconium-containing aerosol antiperspirants contain particles in the respirable range, zirconium-aluminum-glycine complex-containing particles can enter the body. Over the course of years this quantity of zirconium-aluminum-glycine or zirconium-aluminum complex may accumulate and produce undesirable effects other than lung granuloma. The Panel cannot predict exactly what the effects will be, if any, from long term, low-dose inhalation of zirconium-aluminum-glycine complex or zirconium-aluminum complex particles. There is no risk to the lungs or to the internal organs when antiperspirant drug products including zirconium-aluminum-glycine complex are applied as creams or roll-ons, since the intact skin prevents the entry into the body of virtually all zirconium-aluminum-glycine complex particles.

5. *Effectiveness.* Zirconium-containing aerosol antiperspirants appear to be possibly more effective in laboratory hot room tests than those aerosolized antiperspirants formulated with aluminum chlorhydrate alone. Zirconium-containing aerosol antiperspirants are not more effective than nonaerosolized zirconium-aluminum-glycine complex antiperspirants. Several nonaerosolized antiperspirant drug products formulated with aluminum salts appear to be equally effective as zirconium-aluminum-glycine complex-containing antiperspirants in laboratory tests. There is little evidence that consumers can perceive any difference between any of these products under conditions of actual use.

The Panel concluded that the risks involved in the use of zirconium-containing aerosol antiperspirants are unsupportable in view of the benefits likely to be derived from their use. Safer antiperspirant drug products are available which achieve comparable perspiration control with no risk of pulmonary disease.

P. RECOMMENDATION

The Panel recommends to the Commissioner in light of the preceding discussion, that:

1. All zirconium-containing aerosol antiperspirants be placed in Category II (not generally regarded as safe) and,

2. Because conclusive testing to establish the safety of zirconium-containing aerosol antiperspirants might take years to accomplish, and because in that time millions of consumers would be unnecessarily subjected to risk, the Commissioner should take immediate steps outside of the normal OTC drug review process to stop movement of these agents in interstate commerce until the safety testing has been done adequately to secure the approval of an NDA.

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Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 601(a), 701(a); 52 Stat. 1052–1055, as amended (21 U.S.C. 355, 361(a), 371(a))) and under authority delegated him (21 CFR 2.120), the Commissioner proposes that Parts 310 and 700 be amended as follows:

1. In part § 310, by adding a new § 310.510 to Subpart E to read as follows:

§ *310.510 Use of aerosol drug products containing zirconium.*

(a) Aerosol products containing zirconium have been used in over-the-counter (OTC) drug products as antiperspirants. Based upon the lack of toxicological data adequate to establish a safe level for use and the adverse benefit-to-risk ratio, such aerosol products containing zirconium cannot be considered generally recognized as safe for use in drug products. The benefit from using aerosol drug products containing zirconium is insignificant when compared to the risk. Safer alternative antiperspirant products are available.

(b) Any aerosol product containing zirconium is a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application pursuant to section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD-1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that such preparations are safe for the purpose intended.

(d) Any such drug product shipped in interstate commerce after the effective date of the final regulation that is not in compliance with this section is subject to regulatory action.

2. In Part 700, by adding a new § 700.16 to Subpart B to read as follows:

§ *700.16 Use of aerosol cosmetic products containing zirconium.*

(a) Based upon the lack of toxicological data adequate to establish a safe level for use, aerosol products containing zirconium are considered deleterious substances which may render any such cosmetic product injurious to users.

(b) Any aerosol cosmetic product containing zirconium is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any such cosmetic product shipped in interstate commerce after the effective date of the final regulation is subject to regulatory action.

Because § 330.10(a)(2) of the OTC drug review regulations provides 30 days before all data can be made public, and since such data will be needed to adequately comment upon this proposed regulation, the Commissioner has determined that it is in the public interest to provide 90 days for public comment.

Interested persons may, on or before September 3, 1975, file with the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: May 29, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drug.

[FR Doc. 75–14549 Filed 6–4–75; 8:45 am]

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Appointments: Instructor, Division of Dermatology, University of Miami, College of Medicine, Miami, Florida, 1960–61; Assistant Professor, Division of Dermatology, University of Miami, College of Medicine, Miami, Florida, 1961–62; Assistant Professor, Division of Dermatology, University of Tennessee, College of Medicine, Memphis, Tennessee, 1962–67; Professor and Chairman, Division of Dermatology, University of Tennessee, College of Medicine, Memphis, Tennessee, 1967– ; Associate Dean for Postgraduate and Public Education, University of Tennessee, College of Medicine, 1973– ; Consultant in Dermatology, U.S. Naval Hospital, Memphis, Tennessee, 1962– ; Consultant in Dermatology, Veterans Administration, Memphis, Tennessee, 1962– .

Societies: American Medical Association; Tennessee Medical Association; Southern Medical Association; American Academy of Dermatology and Syphilology, (Fellow); Alpha Omega Alpha; Society for Investigative Dermatology: American College of Physicians (Fellow).

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Offices Held: Alpha Omega Alpha, Beta of Tennessee, Faculty Counselor, 1966–1969; Southeastern Dermatologic Association, Secretary-Treasurer, 1970; Faculty of Medicine, University of Tennessee, College of Medicine, President, 1970–71.

Other Activities: Faculty Senate, University of Tennessee, College of Medicine, 1973; Faculty Advisory Council to the President of the University of Tennessee, Member, 1972– ; Memphis Regional Medical Program, Assistant Director, 1970–73.

Major Committee Activities: House Staff Committee, City of Memphis Hospitals, Chairman, 1968–70; Continuing Education Committee, 1970– ; Curriculum Revision, Phase I Committee, Vice Chairman, 1972; Curriculum Revision, Phase II Committee, 1973.

Other Committee Activities: Tennessee Medical Association, Continuing Education Committee, 1971– ; American Academy of Dermatology:

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Continuing Education Committee, 1972– .

Society for Investigative Dermatology:

Finance Committee, 1971–

Public Relations Committee, 1972–73.

Awards: Faculty Recognition Award, Class of June, 1973. University of Tennessee, College of Medicine.

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Rosenberg, E. W.: Dermatitis Medicamentosa (Drug Eruptions), (Chapter) in Conn, H. F. (ed) Current Therapy, 1971. Philadelphia, W. B. Saunders, pp 547–548.

Rosenberg, E. W.: Who's Out of Date? (editorial) New Eng. J. Med. *284*:850–851, 1971.

Craig, S. R. and Rosenberg, E. W.: Methotrexate-Induced Carcinoma, Arch. Derm., *103*:505–506, 1971.

Rosenberg, E. W.: Fluocinomide: Preliminary Evaluation of a New Topical Corticosteroid, Arch. Derm., *104*:632–633, 1971.

Rosenberg, E. W.: Self Review Conference: A Contribution to Problems of Continuing Education and Peer Review, J. Tenn. Med. Assoc., *65*:101–103, Feb. 1972.

Rosenberg, E. W.: Activities and Resources in Continuing Medical Education J. Tenn. Med. Assoc., *65*:611–614, July, 1972.

Amonette, Rex A., and Rosenberg, E. W.: Infection of Toe Webs by Gram-Negative Bacteria, Arch. Derm., *107*:71–73, Jan. 1973.

Evans, Zoe, Rosenberg, E. W., Rendtorff, Robert, and Robinson, Harry: Ecological Influence of Hexachlorophene on Skin Bacteria, J.I.D., *60*:207–214, 1973.

Rosenberg, E. W.: Treatment of Acne, Brit. Med. Jour., *2*:175, 1973.

Gentry, W. C., Jr., Rosenberg, E. W., Goltz, R. W.: A Clinical Evaluation of 0.05% Desonide Cream, Arch. Derm., *107*:870–872, June 1973.

JOHN WESLEY CLAYTON, JR.

DIRECTOR, CENTER FOR ENVIRONMENTAL TOXICOLOGY

Education

Wheaton College: A.B., Zoology, 1948 (Summa Cum Laude).
Central Michigan College of Education: 1943–1944 (U.S. Navy Reserve Unit).
University of Pennsylvania: A.M., Zoology, 1950.
University of Pennsylvania: Ph.D., Zoology, 1954.

Present position

Director, Center for Environmental Toxicology, The University of Wisconsin.

Dr. Clayton is responsible for the development of the curriculum and research efforts of the Center. He is carrying out research in the field of Inhalation Toxicology with special emphasis on delayed pulmonary hypersensitivity, chronic effects of inhaled anesthetics, and the biological activity of organo-fluorine compounds.

Experience

1969–1971. Director, Environmental Sciences Laboratory, Hazleton Laboratories, Inc.

Dr. Clayton joined the staff of Hazleton Laboratories in January 1969 and was responsible for the technical direction and management of research efforts in the environmental sciences. The specific areas include air pollution studies with animals, respiratory physiology, inhalation toxicology, industrial hygiene, environmental health, aquatic biology, radiobiology, and biochemistry as related to ecology.

1954–1969. Toxicologist (1954–1960) and Assistant Director (1960–January 1969), Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Company.

As toxicologist, Dr. Clayton functioned in a supervisory capacity and reported to the Chief of the Toxicology Section. He planned and supervised experimental work in the field of oral toxicity (1954–1957). This included range-finding studies, acute and subacute oral toxicity. Designed, conducted, supervised, and reported chronic feeding studies for the evaluation of a variety of chemical compounds including pesticides.

From 1957 to 1960, he was responsible for planning and supervision of inhalation studies in the laboratory. Involved in this work were screening studies employing small exposure chambers as well as long-term studies utilizing large exposure facilities. Several publications resulted from this activity. These covered the inhalation toxicity of pyrolysis products of resins, studies to validate a safe working atmosphere of a solvent, and a study which led to the clearance by the U.S. Food and Drug Administration of a gaseous food propellant.

During this period, Dr. Clayton became personally involved in the toxicological study of fluorocarbons. In addition to his own laboratory studies of fluorocarbons, several large manufacturers consulted with him on questions concerning fluorocarbon toxicity. Dr. Clayton also has served as a consultant to the U.S. Navy Toxicology Unit on their chronic inhalation studies with Fluorocarbon 11 and Fluorocarbon 12.

As Assistant Director, Dr. Clayton was responsible not only for laboratory administration (staff of approximately 75) but also research management of five technical laboratory sections which included Toxicology, Pathology, Biochemistry, Physics and Physiology. He approved the reports of all technical activities of these sections submitted to the company management.

Among his research management responsibilities were (a) planning the toxicological research involving chronic feeding, teratogenic, rat reproduction, and wildlife studies, to be conducted by outside laboratories under subcontract and maintaining the necessary liaison; (b) evaluation and presentation of results of chronic toxicity studies to the U.S. Food and Drug Administration in support of food additive petitions; (c) consulting with Research, Manufacturing and Sales Divisions of the Industrial Departments of the Du Pont Company on the toxicological aspects of chemical processes and products in the United States, England, and Europe.

Dr. Clayton was the Haskell Laboratory representative to the Du Pont Air and Water Resources Committee, which is a consulting function for the Company in the area of environmental pollution.

1954. Research Associate in Medicine, Jefferson Medical College. Dr. Clayton was responsible for a research program to study the inhalation toxicity of nickel carbonyl. He designed the experiments using an inhalation chamber, and the entailing clinical chemistry, metabolism studies on rats and dogs, and pathological evaluation.

1951–1952. Research Assistant at Penrose Research Laboratory in the Philadelphia Zoo.

1948–1953. Assistant Instructor in Zoology, University of Pennsylvania. While pursuing a program of graduate studies, Dr. Clayton taught courses in zoology, comparative embryology, mammalian anatomy and protozoology. In addition to the research covered in his master's thesis (Oxygen Pressure Effects on Gastrulation and Tail Formation in Rana pipiens), Dr. Clayton was involved in a study of the morphogenesis of explanted amphibian neural crest cells subjected to increased partial pressures of oxygen. His doctoral research involved studies on the cellular division and ecology of termite protozoa.

Professional memberships and affiliations

Air Pollution Control Association.
American Industrial Hygiene Association:
  Member, Hygienic Guides Committee.
  Associate Editor of the AIHA Journal.
American Institute of Biological Sciences.
American Scientific Affiliation.
American Thoracic Society.
Society of Protozoologists.
The Society of Sigma Xi.
Pi Gamma Mu, Social Science Honor Society.
Society of Toxicology:
  Member, Finance Committee.
  Member, Technical Committee.
  Chairman, Technical Committee, 1970–1971.
National Academy of Sciences National Research Council:
  Member, Ad Hoc Committee on Hazard Ratings.
  Member, Sub-Committee on Halothane Anesthetics.
  Member, Committee on Hazardous Materials, Highway Research Board.
Chairman, Gordon Conference on Toxicology and Safety Evaluations, 1970.
Editorial Board, Toxicology and Applied Pharmacology.
State Air Pollution Control Board, Member, Technical Advisory Committee.
Potomac Tuberculosis and Respiratory Diseases Association: Member, Technical Committee.
Northern Virginia Community College: Member, Environmental Sciences Advisory Committee.

JOHN WESLEY CLAYTON, JR.: PUBLICATIONS AND PAPERS

The chronic oral toxicity of manganese ethylene bisdithiocarbamate, Clayton, J. W., Jr., Hood, D. B., Barnes, J. R. and Borgmann, A. R. Presented at the American Industrial Hygiene Association Meeting, St. Louis, Missouri, April 26, 1957.

The toxicity of the pyrolysis products of "Teflon" TFE-Fluorocarbon resins, Clayton, J. W., Jr., Hood, D. B. and Raynsford, G. E. Presented at the Delaware Science Symposium on February 14, 1959 and at the American Industrial Hygiene Association meeting, Chicago, Illinois, May 1, 1959.

Methods used in the evaluation of inhalation toxicity, Clayton, J. W., Jr., Delaplane, M. A. and Hurlbrink, E. E. Presented before the Fourteenth Annual Meeting of the Du Pont Medical Division, October 9, 1959, and at the Delaware Science Symposium, January 13, 1960.

Toxicity studies with octafluorocyclobutane, Clayton, J. W., Jr., Delaplane, M. A. and Hood, D. B. Presented before the 21st Annual Meeting of the American Industrial Hygiene Association, Rochester, New York, April 27, 1960. Published in the Am. Ind. Hyg. Assoc. J. *21*, 382, 1960.

The toxicity of fluorocarbons with special reference to chemical constitution, Clayton, J. W., Jr. Presented at the American Chemical Society Meeting, September 6, 1961. Published in the J. of Occupational Med. *4*, 262, 1962.

The inhalation toxicity of dimethylformamide (DMF), Clayton, J. W., Jr., Barnes, J. R., Hood, D. B. and Schepers, G. W. H. Presented at the American Industrial Hygiene Association Meeting, Washington, D.C., May 17, 1962. Published in the Am. Ind. Hyg. Assoc. J. *24*, 144, 1963.

The investigation of toxicity, Clayton, J. W., Jr. Presented at the fifteenth Annual Meeting of the Du Pont Medical Division, Wilmington, Delaware, September 21, 1962.

Acute toxicity, Clayton, J. W., Jr. Prepared for Lecture on Acute Toxicity, March 26, 1963. Course in Internal Medicine, Graduate School of Medicine, University of Pennsylvania.

The toxicity of organic fluorine compounds, Clayton, J. W., Jr. Presented at the Utah State University, Logan, Utah, August 2, 1963.

The role of industry in chemical ecology, Clayton, J. W., Jr. Presented at the American Industrial Hygiene Association Meeting, New York, N.Y., December 4, 1963.

The pharmacology and toxicology of the environment, Zapp, J. A., Jr. and Clayton, J. W., Jr. Published in Annual Review of Pharmacology *3*, 343, 1963.

Toxicity studies on 1,1,2,2-tetrachloro-1,2-difluoroethane ("Freon-112") and 1,1,1,2-tetrachloro-2,2-difluoroethane ("Freon-112a"), Clayton, J. W., Jr., Sherman, H. Morrison, S. D., Barnes, J. R. and Hood, D. B. Presented at the Society of Toxicology Meeting, Williamsburg, Va., March 10, 1964. Published in the Am. Ind. Hyg. Assoc. J. *27*, 332, 1966.

The toxicity of fluorocarbons, Clayton, J. W., Jr. Presented at the Third International Symposium on Fluorine Chemistry, Munich, Germany, September 2, 1965.

The toxicity of fluoropolymer decomposition products, Clayton, J. W., Jr. Presented at the Interdepartmental Symposium on Fluoropolymers, Du Pont Experimental Station, Wilmington, Delaware, January 14, 1965.

Inhalation studies on chloropentafluoroethane ("Freon-115"), Clayton, J. W., Jr., Hood, D. B., Nick, M. S. and Waritz, R. S. Presented at the American Industrial Hygiene Association Meeting, Houston, Texas, May 6, 1965. Published in the Am. Ind. Hyg. Assoc. J. *27*, 234, 1966.

Fluorocarbon toxicity: past, present and future, Clayton, J. W., Jr. Presented at the Society of Cosmetic Chemists Seminar, September 21, 1966. Published in J. Soc. Cosmetic Chemists *18*, 333, 1967.

The mammalian toxicology of organic compounds containing fluorine, Clayton, J. W., Jr., Chapter 9, *Heffter-Heubner Handbuch der Experimentellen Pharmakologie*, Pharmacology of Fluorides, Vol. XX/1, Springer-Verlag New York, Inc., 1966.

The toxicology of fluoropolymers, Clayton, J. W., Jr., *Heffter-Heubner Handbuch der Experimentellen Pharmakologie*, Pharmacology of Fluorides, Vol. XX/2. In preparation.

Oral toxicity and metabolism of Diuron [3-(3,4-dichlorophenyl)-1,1-dimethyl urea] in rats and dogs, Hodge, H. C., Downs, W. L., Clayton, J. W., Jr., Panner, B. S., Smith, D. W., Maynard, E. A. and Rhodes, R. C., Food Cosmet. Toxicol. *5*, 513, 1967.

Fluorocarbon toxicity and biological action, Clayton, J. W., Jr. Presented at the Symposium of Toxic Effects of Anesthetics, University of Washington, Seattle, Washington, May 13–14, 1967. Published in Fluorine Chemistry Reviews *1*(2), 1967.

Toxicity of Linuron [3-(3,4-dichlorophenyl)-1-methoxy-1-dimethyl urea] in rats and dogs, Hodge, H. C., Downs, W. L., Clayton, J. W., Jr., Panner, B. S., Smith, D. W., Maynard, E. A. and Rhodes, R. C., Food Cosmet. Toxicol. *6*, 171, 1968.

Toxicity of fluorocarbons, Clayton, J. W., Jr., Chapter in *Principles of Aerosol Technology*, edited by Paul A. Sanders, Van Nostrand Reinhold Company, New York, New York. Accepted for publication.

Particulate matter, oxides of sulfur, and sulfuric acid—A Toxicological Appraisal Discussion, Clayton, J. W., Jr., J. of Air Pollution Control *19* (9), 644–646, September 1969.

Histopathological effects of long-term continuous exposure to sulfur dioxide in guinea pigs and cynomolgus monkeys, Busey, W. M., Swann, H. E., Jr., Alarie, Y., and Clayton, J. W., Jr. Presented at the 1970 Meeting of the Soc. of Toxicol.

Chronic inhalation toxicity of a complex mineral oil mist atmosphere, Kwon, B. K., and Waritz, R. S., Clayton, J. W., Jr. Paper presented at the American Industrial Hygiene Conference, Detroit, Michigan, May 11–15, 1970.

Paint vapor hazard under simulated home use conditions, Hornberger, C. S., Kwon, B. K., Clayton, J. W., Jr., and Waritz, R. S. Paper presented at the American Industrial Hygiene Conference, Detroit, Michigan, May 11–15, 1970.

Highlights of fluorocarbon toxicology, Clayton, J. W., Jr., Chapter 21A *Laboratory Diagnosis of Diseases Caused by Toxic Agents*, edited by F. W. Sunderman, M.D., Ph. D., Sc. D., and F. W. Sunderman, Jr., M. D., Warren H. Green, Inc., St. Louis, Missouri, 1970.

Biological effects of sulfur dioxide and fly ash, Clayton, J. W., Jr., EEI R & D Panel for Environmental Improvement, Published in EEI Bulletin, *38*(7), 222–225, 1970.

The effects of chronic inhalation of sulfuric acid mist on primates, Busey, W. M., Alarie, Y., Clayton, J. W., Jr., MacFarland, H. N., Swann, H. E., Jr., and Krumm, A. A. Prepared for publication.

The effects of the chronic inhalation exposure of primates to sulfur dioxide, particulates, and their mixtures, Busey, W. M., Clayton, J. W., Jr., Krumm, A. A., and MacFarland, H. N. Presented at the Air Pollution Control Association, June 1970.

Experimental Neoplasia in Rats from Oral Administration of 3,3′-Dichlorobenzidine, 4,4′-Methylene-bis (2-chloroaniline) and 4,4′-Methylene-bis (2-methylaniline), E. F. Stula, H. Sherman, J. A. Zapp, Jr., J. Wesley Clayton, Jr. Presented at the Annual Meeting of the Society of Toxicology, March 9, 1971, Washington, D.C.

Acute pulmonary reaction to spray starch with soil repellant, Guillermo A. doPico, C. Rodney Layton, Jr., J. Wesley Clayton, John Rankin. Paper presented at the annual meeting of the Wisconsin Thoracic Society, Milwaukee, Wisconsin, April, 1971. (Paper submitted for publication.)

Curriculum Vitae and Publications of Zenona W. Zagula-Mally, M.D.

1. PERSONAL DATA

a. Date of birth: November 18, 1934.
b. Place of birth: Toronto, Canada.
c. Board certified in dermatology (1969).
d. Married, 2 children.
e. Citizenship: American.

2. MEDICAL LICENSURES

a. Ontario, Canada, June 13, 1958, License No. 17225—by examination.
b. Pennsylvania, U.S.A., January 4, 1968, License No. 30018—by examination.
c. Virginia, U.S.A., February 26, 1969, License No. 19653—by reciprocity.
d. Tennessee, U.S.A., October 1, 1970, License No., M.D. 6947. Basic Sciences by examination—Clinical Sciences by reciprocity.
e. California, U.S.A., December 21, 1970, Certificate No. C–33915, by reciprocity.
f. District of Columbia, U.S.A., August 8th, 1973, License No. 3645, by reciprocity.

3. PRESENT POSITION

a. Assistant Professor of Dermatology, University of Tennessee Medical School, Memphis, Tennessee (1969–1973).
b. Attending Physician, Veterans Administration Hospital, Memphis, Tennessee.
c. Co-Project Director, Skin Cancer Study, Memphis, Regional Medical Program.
d. Consulting staff appointment, St. Jude Children's Research Hospital.
e. Principal Investigator of Project No. 69, at the Clinical Research Center entitled "Mitotic Activity of Precancerous Actinic Keratoses and Skin Cancers before and after Topical Chemotherapy".
f. Junior Medical Staff, Baptist Memorial Hospital, Memphis, Tennessee.
g. Dermatology consultant, Memphis State University.

4. EDUCATION

a. Pre-meds, Faculty of Medicine, University of Toronto, Canada (1952–54).
b. Medicine, Faculty of Medicine, University of Toronto, Canada (1954–58).
c. Rotating internship, Toronto General Hospital, Canada (1958–59).

d. Straight medicine internship, Johns Hopkins Hospital, Baltimore, Maryland, U.S.A. (1959–60).
e. Pathology residency, Ontario Cancer Research Institute and the Wellesely Hospital, Toronto, Canada (1960–61).
f. Dermatology residency, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A. (1961–64).

5. EXPERIENCE

a. Medical research and clinical dermatological experience at the dermato-allergy clinic of La Fondation de Rothschild (Chief: the late Dr. Edwin Sidi) 1964–66.
b. Co-authorship, compiling and editing a monograph on Psoriasis (Paris, France and Philadelphia, U.S.A.) 1966–67.

6. APPOINTMENTS

a. Assistant dermatologist, clinical teaching and research, staff position at the Graduate Hospital of the University of Pennsylvania, Philadelphia, July, 1967–68.
b. Present position (See above).

7. SOCIETIES

a. American Academy of Dermatology (fellow).
b. American Association of University Professors.
c. College of Physicians and Surgeons of Ontario, Canada.
d. American Medical Women's Association, Inc.
e. The Society For Investigative Dermatology, Inc.
f. Memphis Dermatological Association.
g. Memphis and Shelby County Medical Society, Inc.
h. American Medical Association.
i. Mid-South Medical Association.
j. American Society of Contemporary Medicine and Surgery.

8. DIPLOMATE

American Board of Dermatology, Nov. 17, 1969.

9. PERSONAL PUBLICATIONS

Books

Sidi, E., Zagula-Mally, Z.W. and Hincky, M.: Psoriasis, Charles C. Thomas, Springfield, Illinois, 1968.

Articles in journals

Zagula, Z.W.J., Maguire, H.C., Jr., and Maibach, H.I.: Dermatitis in Leukopenic guinea pigs. J. Invest. Derm. *41:* 405–411, 1963.
Lowney, E.D., Witkowski, J., Simons, H.M. and Zagula, Z.W.J.: Value of comedo extraction in treatment of acne. J. Amer. Med. Ass. *189:* 1000–1002, 1964.
Sidi, E. and Zagula-Mally, Z.: L'allergie expérimentale de contact chez l' homme et l' animal. Corse-Meditérranée Médicale: *106:* 19–48, 1965.
Reinberg, A. Zagula-Mally, Z. W., Ghata, J. and Halberg, F.: Circadian rhythm in duration of salicylate excretion referred to phase of excretory rhythms and routine, Proc. Soc. Exp. Biol. Med. *124:* 826–832, 1967.
Reinberg, A., Zagula-Mally, Z. Ghata, J. and Halberg, F.: Circadian reactivity rhythm of human skin to house dust, penicillin as well as histamine, J. Allergy *44:* 292–306. 1969.
Zagula-Mally, M.D.: Series of Dermatology Quizzes, *Resident and Staff Physician,* starting April, 1972; *Medical Times,* June, 1972.
Zagula-Mally, Z. W., Rosenberg, E. W., Kashgarian, M.: Frequency of Skin Cancer and Solar Keratoses in a Rural Southern County, as Determined by Population Sampling. *Cancer,* in press.

CURRICULUM VITAE OF JANE M. ROSENZWEIG, M.D.

Born: Detroit, Michigan, February 5, 1937.
Education: Central High School, Detroit, Michigan June 1954; University of Michigan, Ann Arbor, Michigan 1954–1956, University of Michigan Regents-

Alumni Honor Award 1954–55; Wayne State University, Detroit, Michigan 1956–1959, Bachelor of Science; Wayne State University College of Medicine, Detroit, Michigan 1959–1963, Vice-President of Graduating Class.

Internship: Children's Hospital, San Francisco, California 1963–1964.

Residencies: Detroit Receiving Hospital 1964–1965; University of California Medical Center 1965–1967, Chief Resident 1967.

Societies: American Academy of Dermatology; Pacific Dermatological Society; San Francisco Dermatological Society, Vice President 1973.

Teaching posts: Clinical Instructor, University of California Medical Center 1967 to present.

Curriculum Vitae of Eli Shefter

Born September 10, 1936.

ACADEMIC BACKGROUND

1958—B.S. in Pharmacy, Temple University, Philadelphia, Pa.

1962—Ph. D. in Pharmacy, University of Wisconsin, Madison, Wisconsin, Advisor Prof. T. Higuchi.

1962–1964—Postdoctoral Research at University of California at Los Angeles, Chemistry Department with Prof. K. N. Trueblood.

1964–1966—Public Health Service Fellow at Chemical Crystallography Laboratory, Oxford University, England, with Prof. D.C. Hodgkin

1966–1969—Assistant Professor of Pharmaceutics, State University of New York at Buffalo.

1969–present—Associate Professor of Pharmaceutics. State University of New York at Buffalo.

1972–1973—G.A. Pfeiffer fellow of the American Foundation for Pharmaceutical Education—Sabbatical leave at Laboratory for Organic Chemistry, Federal Institute of Technology, Zurich, Switzerland. Collaborated with Prof. J. D. Dunitz.

Professional Organizations (Active Membership)

American Pharmaceutical Association.
American Crystallographic Association.
American Chemical Society.
Chemical Society of England.
Pharmaceutical Society of Japan.
American Association of University Professors.
American Institute of Physics.
Academy of Pharmaceutical Sciences (Elected Fellow).

Present Committee Memberships (Outside University)

United States Pharmacopeia Subcommittee on Analytical Procedures.

Editorial Advisory Committee for the Journal of Medicinal Chemistry (1972 to 1975).

American Association of Colleges of Pharmacy Visiting Lecturer.

Research Interests

X-ray structure analysis of pharmacological substances.
Phase transformation of pharmaceuticals.
Solid state Kinetics.
Holographic analysis: Non-destructive testing of pharmaceuticals.

PUBLICATIONS

1. Shefter, E., and Higuchi, T., Dissolution Behavior of Solvated and Non-solvated Forms of Some Pharmaceuticals, J. Pharm. Sci., *52*, 781 (1963).
2. Shefter, E., Barlow, M., Sparks, R., and Trueblood, K. N., Crystal and Molecular Structure of β-Adenosine-2′-β-uridine-5′-phosphoric Acid, J. Am. Chem., *86*, 1872 (1964).
3. Shefter, E., and Trueblood, K. N. The Crystal and Molecular Structure of D (+)-Barium Uridine-5′-phosphate, Acta Cryst., *18*, 1067 (1965).
4. Shefter, E., and Wolf, W., Crystal and Molecular Structure of 1,3-dihydro-1-hydroxy-3-oxo-benzidoxole, J. Pharm. Sci., *54*, 104 (1965).

5. Shefter, E., and Mautner, H., The Crystal and Molecular Structure of 2,4-Dithiouracil, J. Am. Chem. Soc., *89*, 1249 (1967).
6. Shefter, E., and Kennard, O., Crystal and Molecular Structure of Acetylselenocholine Iodide, Science, *153*, 3742 (1966).
7. Szantay, C., Kotick, M. P., Shefter, E., and Bardos, T. J., Hindered Rotation Around the S–S bond in the Anomeric Di-5-(2′-deoxyuridilyl) disulfides, J. Am. Chem. Soc., *89*, 710 (1967).
8. Shefter, E., and Kmack, G., Phase Transition I: Preliminary Study or the Theophylline Hydrate: Anhydrous System, J. Pharm. Sci., *56*, 1028 (1967).
9. Shefter, E., James, M. N. G., and Mautner, H. G., Crystal Structure of 2,4-Diselenouracil, J. Pharm. Sci., *55*, 643 (1966).
10. Shefter, E., Kotick, M. P., and Bardos, T. J., The Crystal and Molecular Structure of 5-[1-(2′-deoxy-α-D-ribofluranosyl) uracilyl] disulfide, J. Pharm. Sci., *56*, 1293 (1967).
11. Shefter, E., The Crystal Structure of Thiolphthalide, J. Pharm. Sci., *57*, 175 (1968).
12. Shefter, E., Structural Studies on Complexes I: Postulation of Polarization Bonding in Xanthine Complexes, J. Pharm. Sci., *57*, 350 (1968).
13. Shefter, E., and Mautner, H. G., Acetylcholine and Its Thiolester and Selenolester Analogs: Conformation, Electron Distribution, and Biological Activity, Proc. Natl. Acad. Sci. (U.S.A.) *63*, 1253 (1969).
14. Padwa, A., Shefter, E., and Alexander, E., The Correlation of the Crystal and Molecular Structure with the NMR Spectra of a Bicyclo (1.1.1) pentane Derivative, J. Am. Chem. Soc., *90*, 3717 (1968).
15. Shefter, E., Structural Studies on Complexes II: Crystal and Molecular Structure of a 1:1 Caffeine and 5-chlorosalicylic Acid Complex, J. Pharm. Sci., *57*, 1163 (1968).
16. Solo, A. J., Singh, B., Shefter, E., and Cooper, A., Ring D Bridged Steroid Analogues VI: Proof of Stereochemistry and Further Reactions of 14α, 17α-etheno-16α-carbomethoxypregn-5-ene-3β-ol-20-one acetate, Steroids *11*, 637 (1968).
17. Shefter, E., The Crystal and Molecular Structure of a 1:1:1 Complex of Acridine: Cytosine: Water, Science, *160*, 1351 (1968).
18. Shefter, E., The Crystal and Molecular Structure of 6-Thiopurine Riboside, J. Pharm. Sci., *57*, 1157 (1968).
19. Shefter, E., and Kalman, T. I., The Molecular Structure of Disulfide of the t-RNA Constituent, 4-Thioridine, Biochem. and Biophys. Res. Comm., *32*, 878 (1968).
20. Shefter, E., Barlow, M., Sparks, R., and Trueblood, K. N., The Crystal and Molecular Structure of a Dinucleoside Phosphate, β-Adenosine-2′-uridine-5′-phosphoric Acid, Acta Cryst., *B25*, 895 (1969).
21. Shefter, E., Crystallographic Analysis of Drug Molecules, in *Remingtons Pharmaceutical Sciences*, 14th Edition, Mack Publishing Co., Easton, Pennsylvania, Ed. A. N. Martin, 1970, p. 202.
22. Mautner, H.G., and Shefter, E., Studies on the Conformation of Small Molecules Acting on Acetylcholine Receptors, Biological Bulletin, *137*, 388 (1969).
23. Shefter, E., Structural Studies on Complexes IV: Crystal Structure of a 1:1 5 chlorosalicylic acid and Theophylline Complex, J. Pharm. Sci. *58*, 710 (1969).
24. Padwa, A., Battisti, A., and Shefter, E., The Photoisomerization of 9-Thiabicyleo [3.3.1] non-6-en-2-one, J. Am. Chem. Soc., *91*., *91*, 4000 (1969).
25. Shefter, E., and Kalman, T. I., Conformation of Aromatic Disulfides: The Molecular Structure of Ellman's Reagent, Chem. Communication, 1027 (1969).
26. Shefter, E., X-ray Analysis of the Disulfide of 1-Methyl-5-mercaptouracil, J. Chem. Soc., (B), 903 (1970).
27. Pitman, I. H., Shefter, E., and Ziser, M., Covalent Addition of Bisulfite Ion to 2-Amino-1-methylpyrimidinium Ion, J. Am. Chem. Soc., *92*, 3413 (1970).
28. Shefter, E., Sackman, P., Stephen, W. F., and Smissman, E. E., Conformations of Erythro- and Threo-α, β-Dimethyl-acetyl-choline Iodides in the Solid State, J. Pharm. Sci., *59*, 1118 (1970).
29. Mertes, M. P., Powers, L. J., and Shefter, E., Dihydrobenzofurans in Which J cis-2, 3 >J trans-2,3: Confirmation Using X-ray Diffraction Analysis, Chem. Communication, 620 (*1970*).

30. Shefter, E., and Triggle, D. J., Is There a Unique Confirmation of Cholinergic Ligands Responsible for Muscarinic Activity?, Nature, 227, 1354 (1970).
31. Brennan, T. F., Ross, R. K., Hamilton, W .C., and Shefter, E., A Neutron Diffraction Study of an Acetylcholine Analogue: Erythro (±)-α, β-dimethyl acetylcholine Iodide, J. Pharm. Pharmacol. *22*: 724 (1970).
32. Shefter, E., Structural Variations in Cholinergic Ligands, in *Cholinergic Ligand Interactions*, Eds. E. Barnard, J. F. Moran, and D. J. Triggle, Academic Press, New York, 1971.
33. Nelson, W. L., Miller, D. D., and Shefter, E., Acetyl Nitrate Addition to Cyclic Olefins. The Isomeric 9-Acetoxy-10-nitro-1, 2, 3, 4, 4a, 9, 10, 10 a-(trans-4a, 10a)-octa-hydro-phenanthrenes, J. Org. Chem., *35*, 3433 (1970).
34. Shefter, E., and Sackman, P., Structural Studies on Molecular Complexes V: Crystal Structures of Sulfathiazole: Sulfanilamide (1:;) and Sulfathiazole: Theophylline (1:1) Complexes, J. Pharm. Sci., *60*, 282 (1971).
35. Shefter, E., Brennan, T. F., and Sackman, P., Structural Studies on Complexes VI: X ray Investigation of a 2:1 5-Chlorosalicylic Acid: Theobromine Complex, Chem. Pharm. Bull. (Japan) *19*, 746 (1971).
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Microbiology and Immunology Study Section, U.S. Public Health Service 1951–1956, 1957–1958.
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Bacteriology Committee, National Board of Medical Examiners, 1953–1956.
Editorial Board, Journal of Bacteriology, 1951–1955.
Associate Editor, Virology, 1954–1956.
Editorial Committee, Annual Review of Microbiology, 1957–1961.
Member, National Advisory Cancer Council, USPHS, 1958–1959, 1963–1967.
Consultant, National Cancer Institute, USPHS, 1960–1963, 1967–1973.
Member, Program-Project Committee, National Institute of Allergy and Infectious Diseases, USPHS, 1961–1963.
Member, Research Advisory Council, American Cancer Society, 1965–1970; Chairman, 1967–1970.
Vice President, Society of American Bacteriologists, 1958–1959; President, 1959–1960.
Member, Board of Governors, American Academy of Microbiology, 1959–1965; Chairman 1960–1961.
Vice Chairman, Faculty Senate, University of Washington, 1966–1967; Chairman, 1967–1968.
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Publications

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1970: Principal Associate in Biophysics in the Department of Dermatology, Harvard Medical School. 1970: Faculty, Harvard—MIT Health Sciences and Technology—Skin Bio.

Professional and Honorary Societies: American Chemical Society; New York Academy of Sciences; Biophysical Society; Society for Investigative Dermatology; Sigma Xi.

Honors and Awards: American Ceramic Society Ross Coffin Purdy Award for 1960–196—; Citation: For research on the study of dislocation in sapphire crystals. Society of Cosmetic Chemists, Literature Award for 1968. Citation: For studies leading to the elucidation of the mechanism of passage of chemicals through the skin.

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[FDA submissions for the record received by the subcommittee July 24, 1975:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., July 2, 1975.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations and Human Resources, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: This letter is in response to your request for the names of the individuals who concluded to terminate the litigation involving Ornex.

The file on this case shows that this matter was handled by Mr. Eugene Pfeifer and Mr. Alvin Gottlieb.

As Mr. Hutt testified, he delegated all authority on this matter to his staff and told them that they were free to litigate the case or not as, in their judgment, they concluded to be appropriate. At the time that the matter was concluded, Mr. Hutt was not even informed of the outcome. He took this action even though the Department of Health, Education, and Welfare informed him that, as a matter of law, he was not required to disqualify himself on this or any other matter.

Sincerely yours,

ROBERT C. WETHERELL, Jr.,
Director, Office of Legislative Services.

[From the Federal Register, vol. 40, No. 56, Mar. 21, 1975]

PROPOSED RULES ON LAXATIVES

Because of possible drug interaction, the label should contain a statement such as: "Do not use this product if you are currently taking a stool softener laxative." (See dioctyl sodium sulfosuccinate section of this document for explanation).

(ii) *Mineral oil emulsion.* The Panel concludes certain mineral oil emulsions are safe and effective in amounts usually administered orally twice a day with the first dose taken on arising and the second dose taken at bedtime and neither dose at mealtimes (adults 15 to 45 ml of mineral oil component of emulsion, children over 6 years of age 0.25 to 5 ml of mineral oil component of emulsion). Emulsification of mineral oil by magnesium hydroxide or other agents reduces the size of oil droplets, and there is evidence that this property results in enhanced penetration of mineral oil into the fecal mass. Emulsification would theoretically enhance intestinal absorption but the Panel is unaware of evidence that this occurs.

LABELING FOR ORAL PREPARATIONS

The Panel concludes that the labeling which applies to plain mineral oil, should also apply to mineral oil emulsion with the exception of the bedtime ingestion limitation for plain mineral oil. That limitation should be modified to permit a twice daily dosage regimen for mineral oil emulsion with the first dose taken on arising and the second dose taken at bedtime and neither dose at mealtime.

LABELING FOR RECTAL PREPARATIONS

The precautions listed above for oral administration do not apply to rectal administration of mineral oil.

LABELING FOR HEALTH PROFESSIONALS

Professional labeling may contain as additional indications: "For the preparation of the colon for x-ray and endoscopic examination."

Labeling shall contain the following: "Side effects with the proper use of mineral oil are few. However, with chronic use and particularly with excess dosage, excessive laxation, anal leakage and dermatologic reactions may occur. Owing to its property as a lipid solvent, liquid paraffin (mineral oil) may interfere with the absorption of pro-vitamin A, vitamin A, and vitamin D leading to impairment of calcium and phosphorus metabolism. This occurs only under conditions of chronic usage. Administration of mineral oil may lower prothrombin levels, probably secondary to impaired vitamin K absorption, and regular use in pregnancy may predispose to hemorrhagic disease of the newborn. Because of possible interference with nutrition, mineral oil should not be ingested in close proximity to meals. These side effects occur very rarely and then only with chronic and abusive use."

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(e) *Active ingredient classified as a miscellaneous laxative—(1) Released carbon dioxide from combined sodium biphosphate anhydrous, sodium acid pyrophosphate and sodium bicarbonate.* The Panel concludes that rectal suppositories which release carbon dioxide are safe and effective in the amounts usually used rectally once a day as an aid in evacuation of the bowel (no pediatric dosage for children under 12 years).

The suppository dosage form contains 1.2 gm to 1.5 gm sodium biphosphate anhydrous, 0.04 gm to 0.05 gm sodium acid pyrophosphate and 1.0 gm to 1.5 gm sodium bicarbonate, and works through the production of carbon dioxide (approximately 230 ml) in the rectum. The active ingredient, carbon dioxide, is produced by the action of water on these ingredients. The expanding gas induces a gentle pressure in the rectum thereby promoting bowel movement. The suppository should be placed under a water tap for about 30 seconds or immersed in a cup of water for at least 10 seconds prior to rectal insertion.

LABELING

The product should be labeled for rectal use only. To facilitate the release of carbon dioxide, the labeling should state: "Do not lubricate with mineral oil or petrolatum jelly, prior to rectal insertion." In addition, the following warning should be included:

WARNING.—Rectal bleeding, or failure to evacuate may indicate a serious condition and a physician should be consulted.

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2. Conditions under which laxative products are not generally recognized as safe and effective or are misbranded. After carefully reviewing all data submitted as well as additional evidence provided by the Food and Drug Administration and consultants to the Panel and the results of an extensive literature search, the Panel concluded that some OTC laxative ingredients should be removed from the market because of the lack of data supporting their safety. The Panel found

no scientific basis or even sound theoretical reasons for claimed effectiveness of a number of ingredients used in OTC laxatives. In addition, certain labeling claims were considered misbranding. Statements and suggestions that laxatives "improve well being" or "promote good health" are unproven and unacceptable. "Irregularity" as an indication for use is misleading because "regularity" of bowel movement is not essential to health or well being. Laxative products are not appropriate for use solely on the basis of a lack of "regularity," because variability of frequency of bowel movements is normal within the limits referred to elsewhere in this document. All undocumented claims such as "stimulates colonic peristalsis," "acts naturally," and "promotes gentle movements" are unacceptable.

The Panel concludes that the following ingredients, labeling, and combination drugs involved should be removed from the market unless and until further scientific testing supports their use:

ACTIVE INGREDIENTS

Calomel
Carrageenan, degraded
Podophylum resin (podophyllin)
Other laxative resins
  Colocynth
  Elaterin
  Gamboge
  Ipomea
  Jalap

COMBINATIONS WITH NONLAXATIVE ACTIVE INGREDIENTS

Belladonna extract (belladonna alkaloids)
Bismuch subnitrate
Capsicum
Caroid papain
Ginger
Ipecac powder
Thiamin, multivitamin preparations, and minerals

LABELING CLAIMS FOR SPECIFIC INGREDIENTS

Bile acids and ox bile
Dehydrocholic acid
Magnesium compounds

a. *Active ingredients*—(1) *Calomel (mercurous chloride)*. The Panel concludes that calomel is unsafe and unreliable as a laxative.

No data on calomel were submitted to the Panel for review. However, a review of the presently available literature by the Panel requires classification of this compound in Category II and merits special comment, especially with regard to the conclusion that it is unsafe to use as a laxative (Ref. 1).

Calomel is relatively insoluble; however, in the presence of alkali and bile in the intestine, it is oxidized to some extent to mercuric ion, which is responsible for the toxicity of the drug (Refs. 2 and 3). In the event that calomel fails to produce prompt laxation, appreciable amounts of mercury may be absorbed and cause systemic mercury poisoning (Refs. 2, 3, and 4). Autopsies of two women who had been chronic users of calomel-containing laxatives revealed renal tubular and cerebellar damage and chronic colitis. In addition to having kidney failure and necrosis of the colon, the two patients before death had central nervous system manifestations such as personality change and failure of cognition, and at autopsy elevated mercury levels in the kidneys, brain, and colon (Refs. 5 and 6). In infants, administration of calomel has caused a severe febrile (erythematous disease known as acrodynia (pink disease) (Refs. 3, 4, and 7).

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(2) *Carrageenan, degraded (Chondrus crispus, Irish moss).* The Panel concludes that, owing to potential hazards associated with absorbed degraded carrageenan, this material cannot be considered safe on the basis of current evidence.

Native carrageenans which are used in foods possess molecular weights withiin the range of 100,000 to 800,000. If the cross-linkages of the polymer are broken, degraded carrageenans with molecular weights less than 30,000, are formed. In most animal species tested, native carrageenans (See Category III discussion below) are poorly absorbed, but degraded carrageenans are much more amenable to absorption, especially in herbivorous animals. When added to the drinking water of guinea pigs and rabbits, degraded carrageenans caused diarrhea, severe colonic ulceration, hyperplasia of the intestinal mucosa, and weight loss (Refs. 1 through 6). Degraded carrageenan in the drinking water ingested by Rhesus monkeys was extensively deposited in the reticuloendothelial cells and was still present in Kupffer cells 6 months after cessation of carrageenan administration (Ref. 7).

Owing to the observation that degraded carrageenan may inhibit the proteolytic activity of gastric enzymes, the material has been used in man in the treatment of peptic ulcer (Refs. 5 and 9). Because many of these studies were poorly controlled, the significance of these observations is open to question.

The parenteral administrations of carrageenan produces a wide variety of effects. These include, among others, the following: induction of irritation, inflammation, and edema; granuloma formation; release of kinins, probably by activation of the plasmin system; hypotension; anticoagulation; inhibition of complement fixation; and inhibition of immediate and delayed hypersensitivity reactions (Ref. 5).

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(3) *Podophyllum resin* (podophyllin). The Panel concludes that podophyllin is unsafe for use as a laxative because of its potential embryotoxicity and systemic toxicity.

Although podophyllum resin (podophyllin) is official in the U.S. Pharmacopeia (Ref. 1), the ingredient is described only as a cytotoxic agent in the topical treatment of condylomata acuminata (Ref. 11).

Podophyllin and its chief constituent, podophyllotoxin, interfere with normal cell division in animals (Refs. 2 through 4). Because of its inhibitory effect on dividing cells, there is concern that podophyllin may produce an adverse effect on the human embryo and/or fetus. A number of investigators have tested podophyllin or podophyllotoxin in pregnant mice and rats (Refs. 4 through 8) and have demonstrated that these drugs cause a significant incidence of fetal resorption (mortality) and/or fetal growth retardation and that podophyllotoxin interrupts pregnancy in rabbits (Ref. 5). Thus, podophyllin is considered to be a strong embryocidal and fetal growth retarding agent in animals (Ref. 7).

However, the drug has not been shown to produce a significant incidence of gross morphologic (teratogenic) defects in animal fetuses (Refs. 4 through 8). Similarly, the clinical evidence that podophyllin has teratogenic properties in man is equivocal. According to one clinical report (Ref. 9), a patient ingested herbal "slimming" tablets during the first trimester of pregnancy and eventually delivered a baby having multiple deformities involving the thumb, radius, and ear. The "slimming" tablet contained in addition to podophyllin (30 mg), three other plant extractives whose teratogenic potential is unknown. In another case (Ref. 10), severe peripheral neuropathy and intrauterine death occurred in a young woman in the 32d week of pregnancy following the application of podophyllin (1.8 gm) to the vulva for the treatment of warts.

Podophyllin is reported to possess a high systemic toxicity (Ref. 11). For example, in one study, the oral LD_{50} of podophyllin in mice was found to be 68 mg/kg, and the subcutaneous LD_{50} of podophyllin in rats was determined to be 24 mg/kg (Ref. 12). Symptoms of podophyllin-induced toxicity in animals include diarrhea, acute enteritis, rapid and labored breathing, hindlimb paralysis, and convulsions (Ref. 12). Because of the well documented toxic effects of podophyllin in animals and because podophyllin has the potential to cause significant embryotoxicity and systemic toxicity in man, the Panel concludes that this drug is unsafe for use as a laxative.

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(4) *Other laxative resins* (*colocynth, elaterin, gamboge, ipomea, jalap*). The Panel concludes that these plant products are unsafe for use as laxatives because of their potential toxicity.

These plant resins contain active ingredients (usually glycosides) which are released in the intestines. These plant principles are profoundly irritant to the intestines and produce profuse watery stools, which may be blood-tinged, and cause considerable colic (Refs. 1 through 3). Overdose may lead to severe prostration (Ref. 1). Because of the strong action of these irritant principles on the small intestine, their injudicious and long-continued use may lead to nutritional deficiencies, potassium depletion and dehydration (Refs. 1 through 3).

Although these resinous laxatives are not widely used today, the Panel is aware that some OTC laxative mixtures contain these products (Ref. 4). There are no adequate clinical studies to demonstrate that there are safe and effective laxative doses of these irritant resins.

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b. *Combinations with nonlaxative active ingredients.* Some OTC laxative products contain nonlaxative ingredients which do not contribute to laxation and in some instances, greatly increase risk of side effects. Other products contain nonlaxative active ingredients for which the Panel can find no scientific or medical rationale. The Panel concludes that the following nonlaxative active ingredients in combination with laxatives are irrational combinations and are not appropriate therapy for a significant portion of the population.

(1) *Combinations containing nonlaxative active ingredients that increase the likelihood of side effects and/or reduce the safety of the product.—Belladonna extract* (*belladonna alkaloids*). The Panel concludes that the use of belladonna extract or other anticholinergic agents in combination with oral laxatives constitutes irrational and unsafe therapy.

Belladonna extract, which is extracted from the leaves of *Atropa belladonna*, contains atropine and other anticholinergic alkaloids (Ref. 1). The usual quantity of belladonna extract contained in a unit dose of a product is 8 milligrams (equivalent to 0.1 milligram belladonna alkaloids). Belladonna extract is sometimes

combined with laxative mixtures containing anthraquinone compounds, presumably to counteract potential griping action of these laxatives (Ref. 2). However, due to short duration of action (2 to 3 hours) of belladonna extract, the use of this anticholinergic plant drug for this purpose is irrational because its antispasmodic action on the intestine will have subsided before the laxative action (18 to 24 hours) of the anthraquinone is manifest (Refs. 2 and 3).

The addition of belladonna extract to laxative products increases the risk of toxic side effects. The Panel is aware of serious poisoning in children who accidentally ingested laxatives that contain belladonna alkaloids (Ref. 4).

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(2) *Combinations of laxative and non-laxative ingredients for which there is no medical or scientific rationale.*

(i) *Bismuth Subnitrate.* The Panel concludes that the use of bismuth subnitrate or other bismuth salts in combination with laxatives constitutes irrational therapy.

There is no scientific evidence to indicate that bismuth salts contribute to the efficacy or safety of laxative preparations. Bismuth is considered in some textbooks as an astringent and adsorbent, and is discussed by the Panel under antidiarrheals.

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(ii) *Capsicum.* The Panel concludes that the addition of capsicum to laxative products is irrational therapy.

Capsicum is said to be a colonic irritant that produces a sensation of heat (Ref. 1); the agent does not produce cutaneous hyperemia. The use of capsicum as a carminative is based entirely on subjective evidence. The Panel is unaware of any scientific data or even sound theoretical reasoning to indicate that capsicum should be considered an active laxative agent.

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(iii) *Caroid-papain.* The Panel concludes that the addition of caroid-papain or other proteolytic enzymes to laxative agents is irrational therapy.

Caroid-papain, derived from *Carica papaya,* is a mixture of proteolytic enzymes containing papain, bromelin, and ficin, which possess the property of digesting collagen (Refs. 1 and 2). These agents are thought to be innocuous to viable tissues and hence may be considered safe. The Panel is unaware of any scientific data or even sound theoretical reasoning to indicate that caroid-papain should be considered an active laxative agent.

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(iv) *Ginger.* The Panel concludes that, though this material has found wide use and ready acceptance as an aromatic carminative and flavoring agent, no studies have indicated its effect as a laxative agent.

Ginger, the dried rhizone of *Zingiber officinale,* contains a volatile oil, a nonvolatile mixture of substances possessing pungent principles collectively termed gingerol, and an acrid resin (Refs. 1 and 2). It has been advocated for use in man as a carminative for flatulence (Refs. 2 and 3). In addition, it has been used in

veterinary medicine as a carminative for atonic indigestion as well as spasmodic colic, and has been added to veterinary purgatives to prevent griping (Ref. 1). There is no evidence of which the Panel has been made aware that ginger possesses laxative properties or is active in man.

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(3) Glatzel, H., "Treatment of Dyspeptic Disorders with Spice Extracts," Hippokrates, 40:916, 1959 (Ger.).

(v) *Ipecac powder.* The Panel concludes that the use of ipecac in any amounts in combination with laxatives constitutes irrational therapy.

Powdered ipecac, which is obtained from the plant *Cephaelis ipecacuanha* contains a number of emetic alkaloids, including emetine and cephaeline (Ref. 1). Powdered ipecac is now added to some laxative mixtures that contain belladonna extract, on the assumption that the emetic will induce vomiting in the event of an overdose of the laxative mixture. The Panel concludes this is irrational therapy. Furthermore, the quantity of powdered ipecac used in OTC laxative products would not provide an emetic dose, even if 100 dosage units of the laxative product were ingested (Ref. 1).

REFERENCES

(1) The Pharmacopeia of the United States of America, 18th Rev., The United States Pharmacopeial Convention, Inc., Mack Printing Co., Easton, PA, p. 345, 1970.

(vi) *Thiamin, multivitamin preparations, and minerals.* The Panel concludes that the addition of various vitamins and minerals, including trace elements, to laxative products is irrational concurrent therapy and places such combinations in Category II.

An extensive review of the available literature failed to reveal any evidence that the addition of various vitamins, minerals, and trace elements to laxative preparations contribute to a laxative effect. The Panel does not recognize any significant target population that requires laxatives and vitamins concurrently. The Panel does not recognize the use of vitamins for purposes of laxation or the inclusion of vitamins in laxative products as adjunctives to the laxative action of the product. The Panel further concurs that constipation and vitamin needs ordinarily bear no relationship to each other. The rationale of addition of vitamins and minerals intended as nutritional supplements becomes questionable due to the laxative action abrogating the bioavailability of the supplement.

Data in one study in which a combination laxative product containing thiamin was compared with control (no laxatives) are unconvincing in terms of supporting the effectiveness of the combination product, and no evaluation of thiamin alone was undertaken (Ref. 1).

The Panel concludes that the concurrent use of vitamins in OTC laxative products is irrational therapy.

REFERENCES

(1) Long, A. E., "Postpartum Bowel Function," Obstetrics-Gynecology, 11:415-420, 1958.

c. *Labeling claims for specific ingredients.* The Panel concludes the following labeling claims are untrue and represent misbranding.

(1) *Dehydrocholic acid.* There is no evidence in support of the claim that dehydrocholic acid relieves's indigestion, excessive belching, after meal discomfort or the sensation of abdominal fullness. These claims constitute mislabeling and dehydrocholic acid is placed in Category II with respect to these claims. (See discussion of dehydrocholic acid which appears above in stimulant laxative statements.)

(2) *Bile salts (acids and ox bile).* Claims that these agents will "relieve headaches and biliousness" due to constipation are misleading and undocumented. Bile acids and ox bile are placed in Category II for these claims. (See discussion of bile salts (acid) and ox bile which appears below in claimed laxative active ingredients in Category III.)

(3) *Magnesium hydroxide.* Magnesium hydroxide is occasionally promoted as both an antacid and a laxative. This dual claim is permissible owing to the activity of this compound, but the public should be aware that when used regularly as an antacid, magnesium hydroxide causes significant laxation. However, the Panel is not aware of any scientific data that establishes a relationship between acid secretion and constipation. Therefore, claims of superior laxation on the basis of the antacid properties are not acceptable. (See discussion of Magnesium Compounds which appears above in saline laxative statement.)

3. *Conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available to permit final classification of the claimed active ingredients and labeling listed below:

BULK FORMING LAXATIVES

Agar
Bran tablets
Carrageenan, native (Chondrus crispus)
Guar gum

STIMULANT LAXATIVES

Aloin
Bile salts (acid) and ox bile
d-Calcium pantothenate
Frangula
Prune concentrate dehydrate and prune powder
Rhubarb, Chinese
Sodium oleate

SALINE AND HYPEROSMOTIC LAXATIVES

Tartaric acid and tartrate preparations

STOOL SOFTENERS

Poloxalkal (polykol)

LABELING CLAIM FOR SPECIFIC INGREDIENT

Malt soup extract

The Panel believes it reasonable to allow 2 years for the development and review of evidence to permit final classification of these ingredients and the claims made for them. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed as active ingredients in over-the-counter products but may be permitted as inactive ingredients if the amount employed is necessary for the pharmaceutical formulation of the product. Some ingredients may be present in products in quantities which are pharmacologically inactive by virtue of being subclinical doses. In these cases the ingredients may be included for pharmaceutical necessity such as improving the stability or palatability of the product. However, it is the opinion of the Panel that if an ingredient was originally claimed by the sponsor to be active, it cannot then also be claimed inactive and included for formulation purposes unless the following are documented: the absolute necessity for inclusion in the pharmaceutical formulation, the safety of the quantity in the finished product, and the inactivity of the quantity in the finished product.

The Panel has given careful consideration to the types of studies and types of data to be required for removing a claimed active laxative ingredient from Category III and placing it in Category I. See data required below for laxative ingredient evaluation. In general, to demonstrate effectiveness, the design of the study should have a sound scientific basis (e.g., a randomized, double-blind, cross-over study comparing claimed active ingredients to placebo), the clinical trial should be carefully controlled (e.g., consideration given to selection of subjects representative of general population as well as diet, activity, travel, etc. of subjects being studied), and quantitative measurement of various parameters appropriate for the claimed effects of the ingredient (e.g., stool frequency, stool weight, stool water content, stool consistency, etc.). To demonstrate safety, appropriate toxicological studies in experimental animals (preferably primate) and man are required as outlined elsewhere.

a. *Claimed active ingredients classified as bulk-forming laxatives*—(1) *Agar.* The Panel concludes agar is safe in amounts usually taken orally in laxative products but is unable to document effectiveness when used alone in any dose.

Agar is the dried, hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* and related red algae (Refs. 1 through 3 and 5). It is rich in indigestible hemicellulose, is nonabsorbable, and apparently does not cause irritation to the gastronintestinal mucosa. Agar will absorb at least five times its weight of water at 25° C. On absorbing water, it forms a gel and theoretically increases the bulk of the stool. The claimed mechanism of laxative action is considered to be the mechanical stimulus of distention (Ref. 4). It is a common ingredient in a variety of proprietary laxatives and is probably used as an emulsifying and stabilizing agent. When used in these preparations, the amount of agar is too small to contribute to the laxative effect of the preparation.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
OFFICE OF THE SECRETARY,
April 9, 1974.

Memorandum to: Ted Byers.
From: Gary Yingling.
Subject: Marketing of new drug without NDA taking consideration of OTC review.

On April 4, 1974, we received a complaint from a manufacturer that Lever Brothers was test marketing a drug called AIM (toothpaste).

The labeling clearly shows that it is a drug (anti-cavity claim). There is no new drug application for the product. The basis of a new drug application would be that the base of this product does not contain abrasives and that the NDA studies involve drugs which had abrasives.

The commentor was told that the question of what is and is not a new drug for OTC products has involved the OTC Review but we would consult with the Bureau of Drugs concerning this product pending completion of the OTC Review.

I have attached for your review and consideration a tube of AIM, the Dental Care Kit and a black notebook containing consumer advertising and professional promotional material. The professional material concerns the results of some *in vitro* and *in vivo* studies conducted by Lever Brothers.

I would like to meet with you at your earliest convenience to discuss whether the Food and Drug Administration should take action on this product before the OTC Review is complete.

MEMORANDUM OF CONFERENCE, MAY 10, 1974

Between: Gary Yingling (GCF–1).
And: L. M. Baukin, Director, Division of Regulatory Operations (HFD–310).
Rudolf Apodaca, Division of Regulatory Operations (HFD–316).
Subject: Marketing of OTC New Drug Without Approved NDA—AIM Toothpaste.

By memorandum of April 9, 1974, Mr. Yingling reported on an industry complaint that Lever Brothers is test marketing a drug, AIM Toothpaste, without benefit of an effective NDA. The labeling identifies that the article contains stannous fluoride, and it is represented in its labeling as beneficial in reducing the incidence of cavities.

We discussed the fact that under the DESI review a stannous fluoride dentifrice, containing 0.4% stannous fluoride, was classified as effective. There is an approved NDA for one such product. The product is an OTC drug. There is not a question of safety raised by FDA for such a toothpaste containing up to 0.4% stannous fluoride.

We concluded that there is no basis, from a health consideration standpoint, to single out "me-too" fluoride toothpastes for immediate attention, even though marketed currently without benefit of effective NDA's, pending the orderly review of such products under the OTC drug review program.

L. M. BAUKIN.

THE UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

No. 73-118 R.H.S.

BEFORE HON. ROBERT H. SCHNACKE, JUDGE

VAN W. SMART, PLAINTIFF,

vs.

FOOD AND DRUG ADMINISTRATION, DEFENDANT

REPORTER'S TRANSCRIPT, APRIL 19, 1974

APPEARANCES:

For Plaintiff:
VAN W. SMART, Esquire, In propria persona, 26123 Atherton Drive, Carmel, California 93921.

For Defendant:
JAMES BROWNING, U.S. Attorney. By: Howard Chang, Assistant U.S. Attorney, 450 Golden Gate Avenue, San Francisco 94102.

APRIL 19, 1974

The CLERK. Civil 73-118, Van Smart versus Food and Drug Administration, plaintiff's motion to compel answers to interrogatories, defendant's motion to dismiss or for summary judgment, and for prediscovery conference.

Your appearances, counsel.

Mr. SMART. Van W. Smart, for plaintiff.

Mr. CHANG. Howard Chang, for the United States defendant Food and Drug Administration.

Your Honor, we have several motions on today, and I was just wondering how the Court would like us to proceed.

The COURT. Let's consider the motion to dismiss and for summary judgment and hear from Mr. Smart in connection with his opposition to it.

Mr. CHANG. Did you want me to speak first?

The COURT. Let Mr. Smart indicate why they should not be granted.

Mr. SMART. First, your Honor, I believe that there are a number of causes of action alleged which require evidence, and I am thinking particularly now of the question of notice in connection with whether the government gave good and sufficient notice, as required by the Federal Advisory Committee Act and by the executive order.

Also, the plaintiff alleges a course of conduct on the part of the government to deprive him of his rights to make proper presentations on possible appeals for the monographs.

I have stated in my opposition a number of others. Now, the government bases—As I understand the government's position, they allege that the proper indispensible parties have not been joined in this action.

The COURT. Well, that is obviously so, but I think we can ignore that for the present purposes.

Mr. SMART. Now, more than that, I want to touch upon these matters. The Food and Drug Administration does not have primary jurisdiction over OTC drugs. The government has gone to some length in its motion reciting cases that have to do with new drugs. But we are dealing here in this case with OTC drugs.

Now, an over-the-counter drug is a drug that is so safe and so effective that it is a home remedy that has been known for years. There is no jurisdiction—

The COURT. It has been thought, possibly mistakenly, to be so safe and effective; and Congress is now, as I understand it, inquiring into whether those expectations on over-the-counter drugs have been appropriate.

I take it to be fully within their jurisdiction to make that determination and to establish a procedure for doing so, as they have done here.

Mr. SMART. There are a number of—

The COURT. It is completely appropriate to establish advisory commissions or bodies, as they have done here, and the fact they choose to call the advisory report a monograph, rather than something else, doesn't make it any different from what has been done on many occasions.

Advisory committees are policy-determining groups, whose deliberations are entitled to protection. The Freedom of Information Act was never intended to invade the privacy of discussions of this sort.

The matters requested, to the extent they were identifiable under your first cause of action, were, to the extent you were entitled to them—possibly even beyond that extent—supplied to you. The minutes of the meetings of the panel are clearly not matters that are subject to outside intrusion. When those minutes are incorporated in some future action, it may be different. It is perfectly obvious any definitive action having any potential effect upon you, assuming you have any standing to bring this matter, in any event, is far in the future.

But, in any event, when such matters do occur, you will have every opportunity to contest the validity of the results that are found. You have the opportunity at this stage to contribute whatever it is you wish to contribute to the consideration of the panels or to those who are reviewing the determinations.

It seems to me here we have a very sensible, a very valid, a highly appropriate method of exploring a wide range of things that, if they were to be taken on an item-by-item basis would be impossible ever to handle, and it is only by the kind of approach that has been worked out here that the Congressional purpose can be achieved. It is obviously a proper purpose. It is in my view not only permitted, but a highly desirable method of seeking to achieve the purpose.

So I am afraid I must find, under the matters that are before me, that the motion for summary judgment as to the first count of the Complaint will be granted and that the second count of the Complaint simply fails to state any claim on which relief can be granted.

Mr. SMART. Do I understand, your Honor, your position now takes my whole case from me?

The COURT. Yes, sir.

The motion for summary judgment is granted as to the first count and the motion to dismiss is granted with reference to the second count.

Mr. SMART. Your Honor, I would like you to know at this time that I would like to take an appeal.

The COURT. You have the time permitted for appeal, and the Court of Appeals will consider whatever matters you present. All right.

Thank you, counsel.

The CLERK. Do you want Mr. Chang to prepare an order?

Mr. CHANG. Your Honor, I have two orders that I have prepared. I don't know whether they are satisfactory for the purposes the Court has just indicated. If need be, I can prepare another.

The COURT. They may be lodged.

CERTIFICATE OF OFFICIAL REPORTER

I, Carol James, Official Reporter of the United States District Court for the Northern District of California, 450 Golden Gate Avenue, San Francisco, California, 94102, do hereby certify:

That the foregoing transcript, Pages 1 through 7 inclusive, constitute a true and correct transcript of my shorthand notes taken as such Official Reporter of the proceedings hereinbefore entitled reduced to typewriting.

CAROL JAMES,
Official Reporter to Judge Schnacke.

Dated: May 8, 1974.

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6. Regardless of whether or not any or all of the components of Xerac Alcohol Acne Gel may be generally recognized individually or combined with one another in varying combinations and quantities as safe and effective for use in the treatment of acne, when they are combined together into a new or different formulation, and no published medical or scientific information exists, as here, that formulation is a new drug: i.e., it is not generally recognized among qualified experts as safe and effective for its recommended uses.

7. Xerac Alcohol Acne Gel is a new drug within the meaning of 21 U.S.C. § 321(p), which was introduced into interstate commerce in violation of 21 U.S.C. § 355, since no approval of a new drug application filed pursuant to 21 U.S.C. § 355(b) was or is effective with respect to the drug.

NEW DEVELOPMENTS (MARCH 5, 1973)

U.S. v. *Articles of Food and Drug . . . Cali-trol 80 Medicated*

[¶ 40,837] *United States* v. *Articles of Food and Drug . . . Coli-trol 80 Medicated.* In the United States District Court for the Northern District of Georgia. No. 1413. Filed January 29, 1973.

Drugs—Animal Drugs—Misbranding—Equal Protection.—The Food and Drug Administration did not violate the constitutional principle of equal protection of the laws in adopting a different policy for proceeding against misbranded over-the-counter animal drugs than for proceeding against misbranded OTC drugs for humans, as alleged by a veterinary drug manufacturer. The FDA has a policy of taking no enforcement action against misbranded OTC drugs for humans where lack of efficacy is at issue, pending a category-by-category review of those drugs. OTC animal drugs suspected of lack of efficacy are subject to individual seizure without a prior category review process. Different treatment of different classes of persons is not, in itself, a violation of the right to equal protection. A classification is invalid only when the classification is irrational, arbitrary, or capricious and serves no legitimate purpose. The FDA has a legitimate interest in utilizing its resources as efficiently as possible. To accomplish this purpose, it was reasonable to differentiate between veterinary and human drugs.

See FDC Act § 201(w), Drugs, Cosmetics 1 volume ¶ 71,101.

Drugs—Animal Drugs—Misbranding—Summary Judgment.—The issue of whether or not an animal drug is misbranded and adulterated cannot be decided solely on the basis of the affidavits of experts when those affidavits conflict on whether the drug is generally recognized as safe and effective. Since the drug would not be adulterated or misbranded if it was exempt as an old drug generally recognized as safe and effective, a material issue of fact remained to be resolved. The government's motion for summary judgment was denied.

See FDC Act § 201(w), Drugs, Cosmetics 1 volume, ¶ 71,101.

[*Opinion*]

SMITH, J.: This is a civil in rem action arising under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 et seq., to condemn a quantity of several articles of drug and food. The complaint filed on September 27, 1971, alleges that the articles of Coli-Trol 80 Medicated, F4C–60 Feed Grade, Entrol-S Medicated, Entrol-P Medicated and Mycotrol-P Medicated are drugs which were adulterated and misbranded when introduced into and while in interstate commerce. The complaint further alleges that the article of food Myconox LF Litter and Feed Conditioner was adulterated when introduced into and while in interstate commerce. Section 334, 21 U.S.C. authorizes seizure and condemnation of any drug that is adulterated or misbranded while held for sale after shipment in interstate commerce. Pursuant to Motion of the Court, the United States Marshal for this District seized the drugs and food on September 29, 1971. Thereafter, Maremco, Inc., Springfield, Missouri, intervened and filed a claim to the seized articles and an answer which denied the allegations in the complaint.

Interrogatories have been served by plaintiff and answered by claimant. Plaintiff has moved for summary judgment in this action. The claimant has now filed a motion to dismiss or in the alternative for a stay of proceedings, with suggestions in support thereof, on the ground that it has been denied due process of law.

THE MOTION TO DISMISS

Specifically, claimant argues that the Commissioner of Food and Drugs has adopted a discriminatory procedure with respect to two similar classes of products subject to the Food, Drug and Cosmetic Act, namely, over-the-counter (OTC) drugs for human use and over-the-counter (OTC) drugs for veterinary use, which is so arbitrary, capricious and irrational as to deprive claimant of its Fifth Amendment right to due process of law. This argument is based on the fact that the Commissioner of Food and Drugs has proposed a policy of taking no enforcement action against OTC drugs for human use where lack of efficacy is the issue, pending a category-by-category review of those drugs to determine whether those drugs comply with the Federal Food, Drug and Cosmetic Act, while he has not done the same for OTC drugs for veterinary use.

[*FDA Justification*]

The reason for the Commissioner's taking this approach is fully explained in 21 CFR Part 120 (37 F. R., No. 2 pp. 85–86) and includes: (1) the limited resources of the FDA, (2) the impact on the courts by proceeding on a drug-by-drug basis, (3) the inadequate consumer protection produced by a product-by-product review and case-by-case litigation against each drug and (4) the possible repetition of litigation occasioned by the manufacturers changing the formulation of the drug in question.

The FDA, in response to comments on the aforementioned approach with respect to OTC drugs for human use, explained why OTC drugs for veterinary use were not being treated in a similar manner, to wit:

"It was also suggested in one comment that the Food and Drug Administration had not gone far enough in its OTC drug review, because it has failed to include OTC veterinary medication. It is undoubtedly true that OTC veterinary drugs should be reviewed in the same way as OTC human drugs. Because of limited resources, however, it is impractical at this time to review OTC veterinary drugs, the higher priority must be given to a review of OTC human drugs."

(Federal Register of May 11, 1972.)

[*Equal Protection*]

The Fourteenth Amendment guarantee of "equal protection of the laws" is by its terms a limitation on state action. There is no similar provision per se in the Bill of Rights, applicable to the federal government. However, it is clear that any act by the federal government which would in effect be a denial of equal protection of law would constitute a deprivation of liberty within the ban of the Fifth Amendment due process clause. *Bolling v. Sharpe*, 347 U.S. 497 (1954).

As a general rule laws are to some extent inherently unequal. Almost every statute or governmental regulation involves some disparity in treatment; few statutes affect everyone in the country in the same manner. The usual legislative method is to provide for or regulate various *classes* of persons or property. It is apparent, therefore, that laws are usually based on *classification* of persons or property. Such classifications are not per se violative of "equal protection." The only constitutional requirement is that any disparity in treatment caused by such classification be *reasonable*.

[*Reasonableness Standards*]

The standards traditionally utilized by the courts in determining the reasonableness of a statutory classification are as follows:

(1) Whether the classification itself is a *rational* one; i.e. based upon factors (social, economic, historic, etc.) which justify disparate treatment;

(2) Whether the classification bears a reasonable relationship to a proper legislative purpose, and

(3) Whether all persons within the classes established are treated equally.[1]

Stated another way, it is only the classification which is patently arbitrary and utterly lacking in rational justification which is barred by either the "due process" or "equal protection" clauses. *Flemming v. Nestor*, 363 U.S. 603, 611 (1960); *Williamson v. Lee Optical Co.*, 348 U.S. 483, 489 (1955). Alternatively, a classification or regulation "which is reasonable in relation to its subject and is adopted in the interests of the community is due process." *West Coast Hotel Co. v. Parrish*, 300 U.S. 379, 391 (1937). *See Louisville Gas & Elec. Co. v. Coleman*, 277 U.S. 32 (1928).

[*Human Drug Priority*]

In the instant case the FDA has chosen to establish classifications, based upon priorities and the public interest, with regard to enforcement procedures. The FDA's distinguishing OTC drugs for human use from OTC drugs for veterinary use [2] appears to the court to be entirely reasonable, rational, and in keeping with

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[1] The Supreme Court has employed a stricter test when the classification is based on "suspect criteria" (race) or where the classification restricts some "fundamental" right (voting, speech); the instant case does not involve a consideration of either of those criteria.

[2] Claimant has also included the seized article of food, Myconex LF Litter and Feed Conditioner in its motion. Since that article is not a drug, it is inconceivable that this product can be considered in the same class as an OTC drug, much less an OTC drug for human use.

the public interest whose health and welfare the agency is charged to protect. As indicated by the panel in *Philadelphia Television Broadcasting Co.* v. *FCC*, 359 F. 2d 282, 284 (D.C. Cir. 1966):

"In a statutory scheme in which Congress has given an agency various tools with which to protect the public interest, the agency is entitled to some leeway in choosing which jurisdictional base and which regulatory tools will be most effective in advancing the Congressional objective."

See also Pan American World Airways, Inc. v. *C.A.B.*, 392 F. 2d 483 (D.C. Cir. 1968); *Classified Directory Subscribers Ass'n* v. *Public Service Comm'n*, 383 F. 2d 510 (D.C. Cir. 1967). The Fifth Circuit has emphasized that:

". . . agencies must exert the greatest resourceful, imaginative ingenuity in divising procedures which in a day of ever-expanding dockets will permit the regulatory process to function properly with reasonable dispatch." *FTC* v. *J. Weingarten, Inc.*, 336 F. 2d 687 (5th Cir. 1964).

See also Hill v. *FPC*, 335 F. 2d 355 (5th Cir. 1964). It would appear to the court that in the instant case the FDA has attempted to fashion procedures calculated to achieve precisely the result applauded by the Fifth Circuit Court of Appeals in *Weingarten, supra.*

In the matter *sub judice* claimant does not contend that it has been treated differently than any competitor in his class, i.e. manufacturers of OTC drugs for veterinary use dealing in new animal drugs. Therefore, in conclusion, the court finds that the FDA's review procedure for OTC drugs for human use does not invidiously discriminate against the claimant and is not an arbitrary or capricious classification which denies the claimant due process of law.

THE MOTION FOR SUMMARY JUDGMENT

To reiterate: this is a suit in which the government seeks to condemn five drugs and one food additive shipped in interstate commerce from Missouri to Georgia. The particular substances are set out in paragraph two of the complaint, the first five being the drugs in question, and the last being the food additive. The government contends that the five drugs are subject to seizure and condemnation on two grounds: (1) that the substances were misbranded under 21 U.S.C. § 352(a) and, (2) that they are adulterated under 21 U.S.C. § 351(a), in that they were not properly registered as provided by 21 U.S.C. § 360b(a)(1)A. The government contends that the food additive is subject to seizure and condemnation on the ground that it was not exempted under 21 U.S.C. § 348(a) and/or that no regulation issued permitting its use.

The government has moved for summary judgment [and has] submitted the affidavits of three experts in the field of veterinary medicine in support of its contentions relative to misbranding and adulteration. The government's experts' testimony is highly technical and is composed, in the main, of opinions on the effectiveness of the various components of the drugs and food additive under attack. The claimant has submitted a counteraffidavit by an expert in the field of veterinary medicine which substantially contradicts the testimony of the government's experts. Therefore, since issues of fact remain in the matter *sub judice* the court deems disposition of the matter by summary judgment inappropriate. F. R. Civ. P. 56(c). *Sartor* v. *Arkansas Natural Gas Corp.*, 321 U.S. 620 (1944); *Lovable Co.* v. *Honeywell, Inc.*, 431 F. 2d 668 (5th Cir. 1970); *Liberty Leasing Co.* v. *Hillsum Sales Corp.*, 380 F. 2d 1013 (5th Cir. 1967).

WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, ET AL. *v.* BENTEX PHARMACEUTICALS, INC., ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 72–555. Argued April 17, 1973—Decided June 18, 1973

Respondent drug marketers filed suit for a declaratory judgment that their drugs containing pentylenetetrazol are generally recognized as safe and effective and thus are not "new drugs" within the meaning of § 201 (p) of the Federal Food, Drug, and Cosmetic Act of 1938, as amended. They also sought exemption under § 107(c)(4), the grandfather clause, of the 1962 amendments to the Act. The

Food and Drug Administration (FDA) Commissioner, based on NAS–NRC panel reports, concluded that there was a lack of substantial evidence that the drugs were effective for their intended uses and gave notice of his intention to initiate proceedings to withdraw approval of the new drug applications (NDA's). In light of the FDA's position that withdrawal of approval of an NDA would operate to remove marketing approval for all drugs of similar composition, known as "me-too" drugs, whether or not expressly covered by an effective NDA, the Commissioner invited holders of NDA's for drugs containing pentylenetetrazol "and any interested person who might be adversely affected by their removal from the market" to submit "adequate and well-controlled studies" to establish the effectiveness of the drugs. Only one NDA holder submitted further evidence, which the Commissioner held did not satisfy the statutory standard. He gave notice of intent to issue an order withdrawing approval of the NDA's, and only one NDA holder requested a hearing but filed no supporting data. The Commissioner issued orders withdrawing approval of the NDA's and no appeal was taken. Respondents here all market "me-too" drugs, none of which was expressly covered by an effective NDA. The District Court held that the FDA should resolve the "new drug" and "grandfather" issues in an administrative proceeding. The Court of Appeals reversed and remanded with directions to the District Court to determine whether the challenged drugs may lawfully be marketed without approved NDA's, holding that the FDA has no jurisdiction, primary or concurrent, to decide what is a "new drug" for which an NDA is required. *Held:* The District Court's referral of the "new drug" and "grandfather" issues to the FDA was proper. Pp. 649–654.

(a) While an FDA order denying an NDA and withdrawing one is reviewable by the Court of Appeals under § 505 (h), an order declaring a "new drug" status under § 201 (p) is reviewable under the Administrative Procedure Act by the District Court. Pp. 651–652.

(b) The reach of scientific inquiry under both § 505(d) and § 201 (p) is the same, *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *ante*, p. 609, and it is implicit in the regulatory scheme that the FDA has jurisdiction to decide with administrative finality, subject to judicial review, the "new drug" status of individual drugs or classes of drugs. Pp. 652–653.

(c) The "new drug" and "grandfather" issues are peculiarly suited to initial determination by the FDA with its specialized competence and expertise. Pp. 653–654.

463 F. 2d 363, reversed.

DOUGLAS, J., delivered the opinion of the Court, in which all Members joined, except BRENNAN, J., who took no part in the consideration or decision of the case, and STEWART, J., who took no part in the decision of the case.

Deputy Solicitor General Friedman argued the cause for petitioners. On the briefs were *Solicitor General Griswold, Assistant Attorney General Kauper, Deputy Solicitor General Wallace, Andrew L. Frey, Howard E. Shapiro, George Edelstein,* and *Peter Barton Hutt.*

George F. Toomes argued the cause for respondents. With him on the brief were *Sol E. Abrams* and *C. Ben Bowen.**

OPINION OF THE COURT

MR. JUSTICE DOUGLAS delivered the opinion of the Court.

In this case Bentex and some 20 other firms that market drugs containing pentylenetetrazol filed this suit for a declaratory judgment that their drugs containing pentylenetetrazol are generally recognized as safe and effective, and thus not "new drugs" within the meaning of § 201(p)(1) of the Federal Food, Drug, and Cosmetic Act of 1938, as amended, 76 Stat. 781, 21 U.S.C. § 321(p)(1). They also sought exemption from the new effectiveness requirements by reason of § 107(c)(4) of the 1962 amendments to the Act, known as the "grandfather" clause.

As part of the Food and Drug Administration's (FDA's) Drug Efficacy Study Implementation program, three separate National Academy of Sciences-National Research Council (NAS–NRC) panels reviewed the evidence concerning these drugs, and each concluded that the drug was "ineffective" for the indicated use.

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* *Bruce J. Terris, Joseph Onek,* and *Peter H. Schuck* filed a brief for American Public Health Assn. et al. as *amici curiae* urging reversal.

Briefs of *amici curiae* urging affirmance were filed by *Lloyd N. Cutler, Daniel Marcus,* and *William T. Lake* for Pharmaceutical Manufacturers Assn., and by *Thomas D. Finney, Jr., Thomas Richard Spradlin,* and *Daniel F. O'Keefe, Jr.,* for the Proprietary Assn.

The Commissioner concluded there was a lack of substantial evidence that these drugs were effective for their intended uses and gave notice announcing his intention to initiate proceedings to withdraw approval of the new drug applications (NDA's). FDA had taken the position that withdrawal of approval of an NDA would operate to remove marketing approval for all drugs of similar composition, known as "me-too" drugs, whether or not they were expressly covered by an effective NDA.[1] Accordingly, the notice invited the holders of the NDA's for drugs containing pentylenetetrazol "and any interested person who might be adversely affected by their removal from the market" to submit "adequate and well-controlled studies" to establish the effectiveness of the drugs. See § 505(d), 21 U.S.C. § 355(d). Only one NDA holder submitted further evidence, which the Commissioner held did not satisfy the statutory standard. He thereupon gave notice of intent to issue an order withdrawing approval of the NDA's under § 505(e), 21 U.S.C. § 355(e). Again, all those who might be adversely affected by withdrawal of the NDA's were given the opportunity to participate. Only one NDA holder requested a hearing but filed no data to support it. The Commissioner issued orders withdrawing approval of the three NDA's (35 Fed. Reg. 14412); no appeal was taken. This suit in the District Court followed. It appears that all of the parties to this suit market "me-too" drugs, none of which was expressly covered by an effective NDA.

The District Court held that although it could determine whether the drugs were "new" or "grandfathered" drugs, its jurisdiction was concurrent with that of FDA and that FDA should resolve the "new drug" issue in an administrative proceeding. It entered an injunction to preserve the status quo and ruled that if FDA should decline to hold a hearing it would determine the issue. The Court of Appeals reversed and remanded with directions that the District Court determine whether the challenged drugs may lawfully be marketed without approved NDA's. 463 F. 2d 363. It held that FDA has no jurisdiction, either primary or concurrent, to decide in an administrative proceeding what is a "new drug" for which an NDA is required. In its view the 1962 Act established two forums for the regulation of drugs: an administrative one for premarketing clearances for "new drugs" or withdrawal of previously approved NDA's, with the right of appeal; and second, a judicial one for enforcement of the requirement that "new drugs" be cleared as safe and effective before marketing by providing the Government with judicial remedies of seizure, injunction, and criminal prosecution available solely in the District Court. *Id.*, at 371–372.

We reverse the Court of Appeals.

FDA, as a result of an NAS–NRC study and after due notice, faced up to the problem of proposing withdrawal of drugs found to be lacking in substantial evidence of effectiveness. One method would be to have 1,000 withdrawal hearings—perhaps as many as 3,500, each one lasting probably for weeks. The cost in time and budget would be enormous. Accordingly, FDA issued regulations,[2] already discussed in *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *ante*, p. 609, defining the "scientific principles which characterize an adequate and well-controlled clinical investigation,"[3] which elaborates on the statutory "substantial evidence" test. And as we held in *Hynson*, no basis for a hearing under these regulations would be laid unless a party seeking a hearing proffered at least some evidence of that nature and quality.

By May 1972, 102 final orders effecting withdrawal of approval for 452 NDA's had been issued; and they resulted in the removal from the market of an additional 1,473 "me-too" drugs.[4] FDA was still troubled because under the 1962 Act no census of the marketplace was authorized. That is why Congress enacted the Drug Listing Act of 1972, 86 Stat. 559. That Act requires manufacturers to submit to FDA a list of all drugs they market, including data showing their composition, labeling, and advertising.[5] The Senate Report stated: [6]

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[1] Volume 37 Fed. Reg. 23187, adding § 130.40 to CFR, defines "identical, related, or similar drug" as used in this Act to include "other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties." It also provides all persons with an interest in such drugs an opportunity for hearing on any proposed withdrawal of NDA approval for the basic drug. A district court order directing FDA to apply the NAS–NRC evaluation to all "me-too" drugs is reproduced in 37 Fed. Reg. 26623–26624.

[2] 35 Fed. Reg. 3073 and 7250.

[3] See the Appendix in *Hynson*.

[4] Hearings on the Present Status of Competition in the Pharmaceutical Industry before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 92d Cong., 2d Sess., pt. 22, p. 8525.

[5] Filings are due in June 1973. 37 Fed. Reg. 26432.

[6] S. Rep. No. 92–924, p. 2.

"The effective enforcement of the drug provisions of the Act requires the ready availability of a current inventory of all marketed drugs. The Secretary is just completing a thorough review of the effectiveness of drugs marketed pursuant to new drug applications during the period 1938–1962, as required by the Drug Amendments of 1962. Application of the results of this important review to related drugs would be frustrated if a list of all marketed drugs were not easily obtained."

FDA also realized that it is impossible to apply the 1962 amendments to over-the-counter (OTC) drugs on a case-by-case basis. There are between 100,000 and 500,000 of these products, few of which were previously approved by FDA. In May 1972 FDA adopted a procedure for determining whether particular OTC products, not covered by NDA's are safe products, not ineffective, and not misbranded. 37 Fed. Reg. 9464. The procedure involves the establishment of independent expert panels for different categories of OTC drugs (*e. g.*, antacids, laxatives, analgesics) which would review all available data and prepare monographs prescribing drug composition, labeling, and manufacturing controls. OTC's conforming to the monograph will not be considered either misbranded or a "new drug" requiring an NDA. The regulation provides for a hearing before the expert panel, comments and rebuttal comments on the monograph, and finally a hearing before the Commissioner and judicial review. *Id.*, at 9475.

This case, like the cross-petition in the *Hynson* case (No. 72–414) raises the question whether FDA has authority to decide in an administrative hearing whether a drug satisfies the new effectiveness requirements of the Act. As noted, the Commissioner ordered that three NDA's for the drugs in question be withdrawn. Review of the order was not sought in the Court of Appeals as provided in § 505(h), 21 U.S.C. § 355(h). Rather, the aggrieved manufacturers of "me-too" drugs filed suit in the District Court, with the results we have already detailed. The narrow question is whether the FDA may decide whether a drug is a "new drug" on referral from a district court.

As already noted, an order denying an NDA and withdrawing one is reviewable by the Court of Appeals, § 505(h); and we see no reason why Congress could not make one method of review the exclusive one. Certainly an order that does not deny or withdraw an NDA is reviewable under the Administrative Procedure Act, if it declares a "new drug" status. See *Hynson, supra,* at 627. In bolstering that, conclusion we should note in passing that *Abbott Laboratories* v. *Gardner,* 387 U.S. 136, 144, said that the provisions stated in this Act for judicial review do not manifest "a congressional purpose to eliminate judicial review of other kinds of agency action." While § 505(h) would appear to be the exclusive method of obtaining judicial review of FDA's order withdrawing an NDA covering the instant drugs, the Government apparently did not oppose the District Court's taking jurisdiction or appeal from its action and presents no objection to the exercise by the courts of jurisdiction in this case. It does, however, strenuously oppose the conclusions reached by the Court of Appeals.

That court, in holding that FDA has no jurisdiction to determine the "new drug" status of a drug, stated that the question of "new drug" status is never presented when an application of a manufacturer for approval is filed. Parties, of course, cannot confer jurisdiction; only Congress can do so. The line sought to be drawn by the Court of Appeals is FDA action on NDA's pursuant to § 505(d) and § 505(e), on the one hand, and the question of "new drug" determination on the other. We can discern no such jurisdictional line under the Act. The FDA as already stated, may deny an NDA where there is a lack of "substantial evidence" of the drug's effectiveness, based, as we have outlined, on clinical investigation by experts. But the "new drug" definition under § 201(p) encompasses a drug "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use." Whether a particular drug is a "new drug," depends in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by substantial support in scientific literature. One function is not peculiar to judicial expertise, the other to administrative expertise. The two types of cases overlap and strongly suggest that Congress desired that the administrative agency make both kinds of determination. Even where no such administrative determination has been made and the issue arises in a district court in enforcement proceedings, it would be commonplace for the court to await an appropriate administrative declaration before it acted. See *Myers* v. *Bethlehem Shipbuilding Corp.*, 303 U.S. 41, 50–51; *FPC* v. *Louisiana Power & Light Co.*, 406 U.S. 621, 647. It may, of course, be true that in some cases general recognition that a drug

is efficacious might be made without the kind of scientific support necessary to obtain approval of an NDA. But as we indicate in *Hynson, supra,* at 631, the reach of scientific inquiry under both § 505(d) and under § 201(p) is precisely the same.

We think that it is implicit in the regulatory scheme, not spelled out *in haec verba,* that FDA has jurisdiction to decide with administrative finality, subject to the types of judicial review provided, the "new drug" status of individual drugs or classes of drugs. The deluge of litigation that would follow if "me-too" drugs and OTC drugs had to receive *de novo* hearings in the courts would inure to the interests of manufacturers and merchants in drugs, but not to the interests of the public that Congress was anxious to protect by the 1962 amendments, as well as OTC drugs and drugs covered by the 1972 Act. We are told that FDA is incapable of handling a caseload of more than perhaps 10 or 15 *de novo* judicial proceedings in a year. Clearly, if FDA were required to litigate, on a case-by-case basis, the "new drug" status of each drug now marketed, the regulatory scheme of the Act would be severely undermined, if not totally destroyed. Moreover, a case-by-case approach is inherently unfair because it requires compliance by one manufacturer while his competitors marketing similar drugs remain free to violate the Act. In a case much more clouded with doubts than this one, we held that we would not "in the absence of compelling evidence that such was Congress' intention . . . prohibit administrative action imperative for the achievement of an agency's ultimate purposes." *Permian Basin Area Rate Cases,* 390 U.S. 747, 780. And see *Ricci* v. *Chicago Mercantile Exchange,* 409 U.S. 289, 304–306.

We conclude that the District Court's referral of the "new drug" and the "grandfather" issues to FDA was appropriate, as these are the kinds of issues peculiarly suited to initial determination by the FDA. As the District Court said: "Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background." The determination whether a drug is generally recognized as safe and effective within the meaning of § 201(p)(1) necessarily implicates complex chemical and pharmacological considerations. Threshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency, while the court holds its hand. As we stated in *Far Eastern Conference* v. *United States,* 342 U.S. 570, 574–575: "[I]n cases raising issues of fact not within the conventional experience of judges or cases requiring the exercise of administrative discretion, agencies created by Congress for regulating the subject matter should not be passed over. This is so even though the facts after they have been appraised by specialized competence serve as a premise for legal consequences to be judicially defined. Uniformity and consistency in the regulation of business entrusted to a particular agency are secured, and the limited functions of review by the judiciary are more rationally exercised, by preliminary resort for ascertaining and interpreting the circumstances underlying legal issues to agencies that are better equipped than courts by specialization, by insight gained through experience, and by more flexible procedure." And see *Port of Boston Marine Terminal Assn.* v. *Rederiaktiebolaget Transatlantic,* 400 U.S. 62, 68; *Ricci* v. *Chicago Mercantile Exchange, supra,* at 304–306.

Reversed.

MR. JUSTICE BRENNAN took no part in the consideration or decision of this case. MR. JUSTICE STEWART took no part in the decision of this case.

WARNER–LAMBERT COMPANY, PLAINTIFF,

v.

FEDERAL TRADE COMMISSION ET AL., DEFENDANTS.

Civ. A. No. 652–73.

UNITED STATES DISTRICT COURT, DISTRICT OF COLUMBIA.

JUNE 14, 1973.

Action by drug manufacturer to restrain FTC from undertaking further proceedings with regard to cold and sore throat labeling claims of plaintiff's drug and to restrain FDA from further proceeding with its review of all over-the-counter cold remedies, unless the two agencies took appropriate action to prevent conduct of two simultaneous proceedings. On defendants' motion for summary judgment, the District Court, John H. Pratt, J., held that even if dis-

parate actions of FTC, which issued administrative complaint with regard to cold and sore throat labeling claims of drug, and FDA which sought review of all over-the-counter drugs, could be construed as simultaneous duplicative proceedings against a mouthwash preparation, manufacturer had no basis on which to maintain action to restrain these agencies from undertaking further proceedings, where action was neither unlawful not arbitrary and capricious.

Motion granted.

1. Drugs and Narcotics ⇐23

Drug manufacturer did not have standing, in proceeding to restrain FTC from undertaking further proceedings with regard to the labeling claims of drug and to restrain FDA from further proceeding with its review of over-the-counter cold remedies, to challenge memorandum of understanding which was issued jointly by the FTC and FDA and which was promulgated primarily for convenience of agencies in carrying out their functions under two different statutes. Federal Trade Commission Act, §§ 1 et seq., 5. 15 U.S.C.A. §§ 41 et seq., 45; Federal Food, Drug, and Cosmetic Act, § 1 et seq., 21 U.S.C.A. § 301 et seq.

2. Drugs and Narcotics ⇐27

Proceedings by FDA to review all over-the-counter drugs and by FTC against one such drug were not within provisions of memorandum of understanding which was issued jointly by FTC and FDA and by which these agencies agreed to limit proceedings where FTC would file a complaint seeking a cease and desist order on basis of false and misleading claims and where FDA would initiate a seizure proceeding seeking to condemn product on same grounds.

3. Administrative Law and Procedure ⇐315

Same issues and parties may be proceeded against simultaneously by more than one agency.

4. Drugs and Narcotics ⇐10

Trade Regulation ⇐746

Concurrent FDA-FTC proceedings involving same or similar matters are proper.

5. Drugs and Narcotics ⇐10

Trade Regulation ⇐746

Statutory remedies of the FDA and FTC are cumulative and not mutually exclusive. Federal Trade Commission Act, §§ 1, 5, 15 U.S.C.A. §§ 41 et seq., 45; Federal Food, Drug, and Cosmetic Act, § 1 et seq., 21 U.S.C.A. § 301 et seq.

6. Drugs and Narcotics ⇐23

Even if disparate actions of FTC, which issued administrative complaint with regard to cold and sore throat labeling claims of drug, and FDA, which sought review of all over-the-counter drugs, could be construed as simultaneous duplicative proceedings against a mouthwash preparation, manufacturer had no basis on which to maintain action to restrain these agencies from undertaking further proceedings, where action was neither unlawful nor arbitrary and capricious. Federal Trade Commission Act, §§ 1 et seq., 5, 15 U.S.C.A. §§ 41 et seq., 45; Federal Food, Drug, and Cosmetic Act, § 1 et seq., 21 U.S.C.A. § 301 et seq.

H. A. Bergson and Arthur B. Wineburg, & Adler, Margolis Borkland, Bergson, Washington, D.C., for plaintiff.

Robert M. Werdig, Jr., Washington, D.C., for defendants.

MEMORANDUM OPINION AND ORDER

JOHN H. PRATT, District Judge.

This matter is before the Court for consideration of defendants' motion for summary judgment. Upon consideration of the complaint, the motion of defendants for summary judgment, the opposition of plaintiff thereto, and it appearing to the Court that there is no genuine issue as to any material fact, the motion of defendants for summary judgment is granted, based upon the following:

Plaintiff, Warner-Lambert Company (hereinafter referred to as "Warner-Lambert"), is engaged in the manufacture, advertising, labeling and sale of the mouthwash preparation Listerine Antiseptic (hereinafter referred to as "Listerine").

The Federal Trade Commission (hereinafter referred to as "FTC") is an administrative agency of the United States established by the Federal Trade Commission Act, 15 U.S.C. § 41 et seq. for the purpose, *inter alia*, of preventing unfair methods of competition and unfair and deceptive acts and practices.

Individual defendants, Engman, Dixon, MacIntyre, Jones and Dennison are commissioners of the FTC.

Individual defendants Weinberger and Gardner (hereinafter referred to collectively as "FDA") are the Secretary of Health, Education and Welfare and the Acting Commissioner of Food and Drugs, respectively.

The Secretary and Commissioner are responsible, *inter alia*, for the enforcement of the Federal Food, Drug and Cosmetic Act. 21 U.S.C. § 301 et seq.

Preliminary Statement

This action seeks to restrain the Federal Trade Commission from undertaking further proceedings in FTC Docket No. 8891, and to restrain the Secretary of Health, Education and Welfare and the Commissioner of Food and Drugs from further proceeding with its review of over-the-counter cold remedies, unless and until the two federal agencies take appropriate action to prevent the conduct of two simultaneous proceedings with regard to the cold and sore throat claims of Listerine Antiseptic. The action further seeks to restrain the Federal Trade Commission from undertaking further proceedings in FTC Docket No. 8891 with regard to the cold and sore throat labeling claims of Listerine Antiseptic.

A.

The FTC Proceeding

Plaintiff is the respondent in an adjudicative proceeding presently pending before the FTC under FTC Docket 8891. The proceeding was initiated by issuance of an administrative complaint on June 27, 1972. A copy of the administrative complaint is attached to Warner-Lambert's complaint as Attachment A.

The complaint, in general, alleges Warner-Lambert, in its advertising, offering for sale, sale and distribution of the mouthwash preparation Listerine to retailers for resale to the public, has misrepresented by false, deceptive and misleading statements the effect of the product in the prevention, cure, treatment and mitigation of colds and sore throats. The false, deceptive and misleading statements were, it is averred, made on packages or labels, printed advertisements, and television commercials.

The allegations of the complaint also state Warner-Lambert has falsely represented that the use of Listerine would make colds milder or less severe, by relieving or lessening the severity of cold symptoms to a significant degree. It is also stated Warner-Lambert has misrepresented that its most recent test results and studies prove or support the representation that children "who gargle with Listerine twice a day have fewer and milder colds and miss fewer days of school because of colds than do those children who do not gargle with Listerine twice a day."

The complaint further alleges Warner-Lambert, through the use of the statement "Kills Germs by Millions on Contact," represents, contrary to fact, that the ability of Listerine to kill germs is of medical significance in the prevention, cure or treatment of colds and sore throats. Such representations, the complaint states, have the capacity and tendency to mislead the purchasing public into the purchase of substantial quantities of Listerine to the injury of the public and in violation of Section 5 of the Federal Trade Commission Act (15 U.S.C. § 45).

Warner-Lambert, on August 30, 1972, filed an answer denying the substantive averments of the FTC complaint (Attachment B to the complaint). Hearings before the Administrative Law Judge have been scheduled to commence on September 24, 1973.

B.

The FDA Proceeding

Recognizing that self-medication is essential to the nation's health care system, FDA has concluded: it is "imperative that over-the-counter drugs available for human use be safe and effective and bear fully informative labeling" and a substantial number of the 100,000 to 500,000 over-the-counter drugs on the market do not have their claimed effect. 37 Fed. Reg. 85 (1972). Because of the inadequacy, great cost, and burden on the courts of proceeding against individual drugs on a case-by-case basis, the Commissioner of Food and Drugs, on December 30, 1971, proposed new regulations setting up a procedure for a thorough and complete review of all over-the-counter drugs. 37 Fed.Reg. 85 (1972).

The proposed regulations were published in final form on May 11, 1972.[1] An advisory panel of qualified experts, for each of 26 categories of over-the-counter drugs, upon consideration of, *inter alia*, data submitted by drug manufacturers relating to the safety and effectiveness of the drug involved, will submit to the Commissioner a report containing its conclusions and recommendations with respect to the category of drug it has reviewed. Included in this report will be a recommended monograph, which shall establish the conditions under which the drugs involved are generally recognized as safe and effective and not misbranded. 21 C.F.R. 130.301(a)(1)–(5). 37 Fed.Reg. 9474 (1972). Thereafter, the Commissioner shall publish: (1) a proposed monograph, after which comments are invited; (2) a tentative final monograph, following a review of the comments received; and (3) a final monograph, following a review of the objections of the tentative final monograph and a consideration of any oral hearing before the Commissioner, if any. The final monograph constitutes final agency action from which appeal lies to the courts. 21 C.F.R. 130.301(a)(10). Any product which fails to conform to the final monograph is liable to regulatory action. 21 C.F.R. 130.301(a)(12), 37 Fed.Reg. 9475 (1972).

Advisory panels of experts for certain of the categories of OTC drugs have already convened. One proposed monograph, relating to antacid drugs, has been published. 38 Fed. Reg. 8714 (1973). With respect to cold remedies, Listerine is one of many products to be reviewed. No monograph has yet been proposed. An invitation for all interested persons to submit data bearing on the safety and effectiveness of the ingredients of cough-cold-remedies was published on August 9, 1972. 37 Fed. Reg. 16029. The purpose of FDA's request is to gain information seeking to establish product standards applicable to the entire industry. As a nonprescription cough and cold remedy, Listerine will be subject to the requirements of any monograph issued by FDA pursuant to the rulemaking proceedings.[2]

C.

Plaintiff argues the two proceedings complained of are unlawful in that they violate a "rule" of both agencies. The "rule" which plaintiff asserts is binding upon defendants is a "Memorandum of Understanding" issued jointly by FTC and FDA and published at 36 Fed. Reg. 18539 (1971). Plaintiff's contention is erroneous. Even assuming, arguendo, the "rule" is binding on defendants,[3] it is clear it does not apply to the proceedings in issue.

[1] The Memorandum is an agreement between the two agencies promulgated primarily for the convenience of the agencies in carrying out their functions under two different statutes. The only parties to the agreement were the two agencies involved, and an individual private party, such as plaintiff, may not invoke the agreement in challenging these agency actions. Furthermore, in the Court's opinion, the agreement has not been breached. It is apparent from the affidavits of Messrs. Freer and Fine filed with the Court on May 1, 1973 that there was considerable liaison resulting in an express agreement between the two agencies sufficient to satisfy the requirements of the Memorandum of Understanding.

As far as the proceedings themselves are concerned, it is the Court's opinion they are quite different. As has been pointed out previously, the proceeding before the Federal Trade Commission is an adversary proceeding. It is an adjudicatory proceeding. It involves only Warner-Lambert.

The proceeding before the Food and Drug Administration is a rule-making proceeding. It involves thousands of manufacturers of over-the-counter products, including cold remedies. It is a proceeding which individual companies can participate in or decline to participate in, at their option, recognizing it may also be to their possible disadvantage.

If this Court were to require the Food and Drug Administration to exempt plaintiff from its proceeding, it seems such action would give plaintiff a discriminatory preference over the manufacturers of many products of a similar kind, namely, over-the-counter cold remedy products.

[2] The joint proceedings which FDA and FTC agreed to limit were intended to be proceedings where the FTC would file a complaint seeking a cease-and-desist order on the basis of false and misleading claims, and where the FDA would

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[1] "Over-the-Counter (OTC) drugs for human use; procedures for rulemaking . . ." 37 Fed. Reg. 9473.

[2] *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 87 S. Ct. 1507, 18 L. Ed. 2d 681 (1967); *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466 (2 Cir., 1971).

[3] The informality of the agreement is evident in that by its express terms the Memorandum of Undedstanding may be terminated by either party upon thirty days' notice.

institute a seizure proceeding seeking to condemn the product on the same grounds. It is certain that the present proceedings, i.e., the FDA review of all OTC drugs, and the FTC complaint against *one* OTC drug, are not within the provisions of the Memorandum of Understanding. For if this were the case, then the FTC would now be foreclosed from proceeding against any of the 100,000 to 500,000 OTC drugs currently on the market, no matter how false or how misleading the claims for such a product.

D.

[3] The Supreme Court has long held that the same issues and parties may be proceeded against simultaneously by more than one agency. FTC v. Cement Institute, 333 U.S. 683, 68 S.Ct. 793, 92 L.Ed. 1010 (1948); United States v. W. T. Grant Company, 345 U. S. 629, 631–632, 73 S.Ct. 894, 97 L.Ed. 1303 (1953); United States v. Radio Corporation of America, 358 U.S. 334, 343–344, 79 S.Ct. 457, 3 L.Ed.2d 354 (1959); FTC v. Motion Picture Advertising Service Company, 344 U.S. 392, 73 S.Ct. 361, 97 L.Ed. 426 (1953); United States v. Borden Company, 347 U.S. 514, 74 S.Ct. 703, 98 L.Ed. 903 (1954). In FTC v. Cement Institute, *supra* the defendant sought dismissal of the FTC proceedings on the basis that the Department of Justice had proceeded against them in District Court under the Sherman Act. The defendant, as plaintiffs do here, asserted that it was against the public interest to defend both the FTC proceeding and the Sherman Act proceeding which were based on the same alleged misconduct. The Supreme Court, in a holding that has been followed many times, stated that the Sherman Act and the Federal Trade Commission Act provide the Government with cumulative remedies which are not mutually exclusive.

[4, 5] These same principles apply to the concurrent actions of FDA and FTC which may involve the same parties or issues. The propriety of simultaneous FDA–FTC proceedings involving the same issues does not, as claimant would have this Court believe (Complaint, par. 17), present a novel legal issue. For in at least three cases, the courts, including this Court, have held that concurrent FDA–FTC proceedings involving the same or similar matters are proper, and that the statutory remedies of the two agencies are cumulative and not mutually exclusive. United States v. 1 Dozen Bottles, etc., 146 F.2d 361 (4 Cir. 1944); United States v. 5 Cases . . . Capon Springs Water, 156 F. 2d 493 (2 Cir. 1946); United States v. ". . . Instant Alberty Food . . . .", 83 F. Supp. 882 (D.D.C. 1949).

[6] In the present case, even if the disparate actions of the FTC and FDA could be construed as simultaneous duplicative proceedings against Listerine Antiseptic, it is clear that the action is neither unlawful nor arbitrary and capricious and therefore plaintiff has no basis upon which to maintain this action.

E.

Plaintiff has available administrative remedies before each agency which have not been exhausted. Still to be completed before FTC is the administrative proceeding in which Warner-Lambert will have full opportunity to present evidence and argument in its behalf. If the adjudicative proceedings do terminate in an order against Warner-Lambert to cease and desist, Warner-Lambert has the right to appeal directly to a United States Court of Appeals. Section 5 of the Federal Trade Commission Act, 15 U.S.C. § 45. The Act further provides that the jurisdiction of the courts of appeals "to affirm, enforce, modify or set aside orders of the Commission shall be exclusive." 115 U.S.C. § 45(d). The Act nowhere provides for a review in district courts of interlocutory ruling by the Commission, and 5 U.S.C. § 704 expressly provides: "A preliminary, procedural or intermediate agency action or ruling not directly reviewable is subject to review on the review of the final agency action." Similarly, if FDA issues a monograph at the conclusion of its proceedings, review of that action may be sought in the courts.[4]

Conclusion

Having considered the foregoing, the Court concludes: there is a rational basis for the actions of each of the agencies in initiating and pursuing their individual proceedings; plaintiff does not have standing to challenge, in this action, the Memorandum of Understanding between the agencies; the two agencies

[4] 21 C.F.R. 130.301(a)(10) provides that the monograph contained in the final order constitutes final agency action from which appeal lies to the courts.

complied with the provisions of the Memorandum of Understanding; the proceedings before the two agencies are not duplicative; plaintiff has not exhausted its administrative remedies; there is no evidence of record that plaintiff is required to respond to the proceeding before FDA, although its failure to respond may be at its peril; and there is no indication that it is in the public interest to enjoin the disparate agency proceedings at this stage.

In summary, plaintiff has not met the criteria for the granting of a preliminary injunction and its motion for a preliminary injunction is denied. Count II of the complaint seeking a permanent injunction against FTC maintaining the labeling charges against plaintiff is dismissed and defendants' motion for summary judgment is granted.

The foregoing shall constitute the Court's Findings of Fact, Conclusions of Law, and Order.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY,
May 13, 1975.

Memorandum to: Memorandum to File.
From: Gary L. Yingling (GCF-1).
Subject: Abbreviated New Drug Application for Procter & Gamble's Secret Spray Antiperspirant.

1. The abbreviated NDA was filed on January 10, 1972. The proposed formulation contained 0.3% hexachlorophene which the firm indicated was being removed from the product.

2. Secret spray antiperspirant was being sold nationally on January 10, 1972 in plastic coated glass bottles. It was also being test marketed in limited areas in the conventional metal aerosol cans.

3. The firm indicated that they may be test marketing in the near future a similar product under the brand name, *Sure*. The label and formula would be similar. (Ref: Page of ANDA by P & G).

4. The table of contents for the abbreviated NDA show that the firm submitted information on:

I. Labeling
II. Prescription Use (said not applicable to ANDA)
III. List of Articles Used As Components
IV. Composition of Secret Spray Antiperspirant
V. Manufacturing Procedures
VI. The Appendix which included analytical methods

No data was supplied on safety and effectiveness since the firm was relying on DESI 6615.

5. A copy of DESI 6615 (in ANDA file) (36 F.R. —, September 8, 1971.) states that four antiperspirant/deodorants for topical use (Ice Blue Secret Cream Deodorant, Ice Blue Secret Roll-On Deodorant, Old Spice Spray Deodorant, and Veto Cream Deodorant) were reviewed. Of these four, only the Ice Blue Secrets contained zirconium. Old Spice Spray Deodorant contained dibromsalan and Veto contained aluminum sulfamate. The notice said that these were new drugs and that supplemental new drug applications were required to revise the labeling in and update approved applications providing for such products. New drug applications were also required from any person marketing such a drug without approval.

A. *Effectiveness classification.*—said that FDA concluded that preparations containing zirconium oxychloride, aluminum clorhydroxide and hexachlorophene; dibromsalan and aluminum chlorhydroxide; or aluminum sulfamate are *effective* as deodorant/antiperspirants.

B. *Conditions for approval and marketing.*—The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under the conditions described herein.

1. *Form of the Drug.*—These preparations are in a "form suitable" for topical application. (Clearly, the spray form is suitable for topical application and Procter and Gamble seems to be correct in the submission of an abbreviated NDA based on the 6615 DESI Notice).

2. *Labeling Conditions.*

a. The drug is labeled to comply with the Act
b. A statement of identity
c. The indication for use as an antiperspirant or deodorant

3. *Marketing status.*—Marketing of such drugs may continue under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in the Drug Efficacy Study", 35 F.R. 11273, July 14, 1970.

The Notice was dated August 18, 1971 and was signed by Sam D. Fine, Associate Commissioner for Compliance.

6. On January 21, 1972 Marvin Seite, M.D. wrote to Procter & Gamble indicating receipt of the abbreviated NDA application. It was given ANDA No. 80-837.

7. Bureau of Drugs memoranda dated February 17, 1972 by Bruce E. Byer. Mr. Byer sent a request to the Chicago and Newark District Offices asking for an inspection of the two companies doing the manufacturing and packing to determine whether the firm's GMP (130.4f) were in compliance. The Districts were to indicate whether or not the ANDA could be approved based upon the firms' compliance with GMP's. Any recommendation to withhold approval was to be based on critical or significant deviations of the GMP's which should be listed.

8. A memorandum-Review of ANDA was completed March 3, 1972 by Aaron S. Weiner, M.D.

CLINICAL EVALUATIONS

1. Review of Studies: None submitted or *required.* (Note that FDA thought no studies were "required").

2. Review of Labeling:

(*a*) Recommended the following additions to the labeling.

1. Keep away from eyes or other mucous membrane.
2. Avoid inhaling.

Other minor labeling suggestions were made but are not listed.

Conclusions.—Comments on the formulation will be withheld pending removal of hexachlorophene.

RECOMMENDATIONS

1. Request label revisions.
2. Date of Reformulation.
3. Labels for Sure when available.

"Keep away from eyes or other mucous membrane" and "Avoid inhaling" appear to be standard OTC antiperspirant requirements for all *spray* products.)

9. FDA Drug Bulletin dated February 1972. The FDA Drug Bulletin relates to hexachlorophene in drugs, soaps and cosmetics. FDA's recommendation under this bulletin were (1) hexachlorophene may not be used in cosmetic products except as a preservative in levels up to 0.1% and then only when other suitable preservatives are not available, (2) when hexachlorophene is a component of drugs which have approved new drug application, the drug label must read "caution, etc." Hexachlorophene level in such a product may not exceed 0.75%, (3) drugs containing hexachlorophene levels over 0.75% must bear a prescription legend.

10. A handwritten memo containing no signature or date. It indicates the following:

(*a*) Procter & Gamble had two effective NDA's, one was a roll-on effective 12/26/61 (NDA 12-983) and the other a cream effective 1/5/62 (NDA 12-984). The NAS/NRC reviewed both of these NDA's as part of the DESI notice 6615.

(*b*) Previously Procter & Gamble had three *Secret* topical antiperspirants marketed under NDA's. They were for a cream effective June 1, 1956 (NDA 10-461), a roll-on effective on July 16, 1958 (NDA 11-086) and a touch top effective May 20, 1959 (NDA 11-910). These three products were discontinued in 1962 when the firm started using hexachlorophene. They therefore were not subject to the NAS/NRC review. Each one of the above three products contained zirconium hydroxychloride, aluminum hydroxychloride and glycine.

(*c*) FDA notified Procter & Gamble on July 7, 1971 that Secret cream deodorant remained a new drug. The applicant had on November 4, 1971 relative to the Federal Register notice of September 8, 1971, submitted formulation date on Secret cream deodorant and antiperspirant (NDA 12-984). Because the three products with HCP were not marketed, these three NDA's were withdrawn by the Commissioner on August 6, 1971.

(*d*) The memo indicates that Procter & Gamble in ANDA 80-837 had not provided information on a proprietary emollient.

(*e*) Procter & Gamble also failed to provide a specific formulation for the new dry formula Secret Antiperspirant (aerosol can). The aerosol article is different from the two products (NDA 12-983 and 984) referred to in the DESI notice 6615.

(*f*) A statement in the memo says that "In the past the new drug status unit of the Bureau of Medicine has held that the adding of a new spray type aerosol antiperspirant article with gas propellant to products previously marketed under the new drug procedures required a full new drug application to demonstrate the safety and efficacy. In general the so-called topical 'concentrate' reaching the users skin area determined the dermatological evaluation of the article". (There is no discussion of the reasons or whether or not policy had changed prior to or at the time the memo was written).

(*g*) Calculations are done to show that the alcohol level is sufficiently high so that hexachlorophene is not necessary as a bacteriostatic agent.

(*h*) The memorandum raises no serious safety issue but discusses the fact that hexachlorophene is probably not necessary.

11. A letter dated April 28, 1972 is to Procter & Gamble from Marvin Seife, M.D. The first page refers to the changes in labeling which were listed in Dr. Werner's memo of March 3, 1972 and a clarification of the composition of the drug pursuant to the handwritten memo.

(*b*) Included in page 2 is a request that an abbreviated new drug application be limited to one particular formula containing the specific unit dose of each active ingredient. (The application was actually for a squeeze bottle and the aerosol can which resulted in different formulations.)

(*c*) On page 2 in paragraph number 2 there was a request that the certification from one firm as to its GMP's be clarified. Paragraph number 3 requests a clarification of the analytical procedures. (The analytical procedures had failed to include a method for determining the alcohol, chloride content on the product and a bacteriological purity test on the water.)

(*d*) On the last page of the letter, FDA noted that GMP deficiencies would have to be corrected ". . . before we can take further action on the abbreviated new drug application, we should have a satisfactory inspection report."

(*e*) The last paragraph of the letter states that the hexachlorophene issue would be reserved pending reformulation and deliberations of the OTC Panel.

Nowhere in the three page letter did the FDA question the validity of filing an abbreviated new drug application for this drug, even though the issue was raised in a handwritten memorandum. (I am unable to tell from reading this one file whether in fact the handwritten memorandum represents the Bureau's policy at the time.)

12. A June 20, 1972 letter was sent by Paul A. Bryant to Procter & Gamble telling them that their abbreviated NDA would not be reviewed. The letter stated "pursuant to the policy of review of over-the-counter drugs as stated in the Federal Register announcement of April 20, 1972, the material you have submitted will not be reviewed at this time but will be handled by the appropriate OTC panel at a later date. The material you have submitted will be retained in our files." This letter was counter signed by Dr. Clark and Dr. Marvin Seife. (This was clearly the policy within the Agency since no safety issue had been raised. Based on the NAS/NRC DESI No. 6615 it was reasonable at that time to defer consideration of this issue to the OTC Review. There is nothing in the file to indicate that the abbreviated NDA would *not* have been granted if it had not been for the pending OTC review.)

HEW News, *March 20, 1975.*

U.S. Department of Health, Education, and Welfare

Food and Drug Administration

The Food and Drug Administration today made public a report of a panel of non-FDA scientists who have reviewed more than 100 ingredients used in an estimated 25,000 laxative, antidiarrheal, emetic (vomit inducing) and, antiemetic drug products sold on the U.S. market without a prescription. The panel is part of FDA's ongoing review of all over-the-counter (OTC) drugs now being sold.

The expert committee evaluated 101 ingredients used in this group of nonprescription products. Fifty ingredients were judged by the committee to be safe and effective, 30 were rated as needing further study, and 21 were judged either ineffective or unsafe.

Following a period for public comment and FDA evaluation, a monograph (in effect a class standard) will be issued for all products using ingredients reviewed

by the expert panel. When finally issued later this year, the monograph will constitute an official FDA "recipe book" for safe and effective products acceptably formulated and adequately labeled for use without physician supervision.

After the monograph issues, manufacturers whose products contain ingredients judged less than effective will have the option of:

1. reformulating to meet the FDA approved "recipe" for safe and effective ingredients, or,

2. developing scientific justification for continuing to use those ingredients judged by the FDA and its expert advisors as needing further study.

Ingredients finally ruled ineffective or unsafe, and having false or misleading label claims must be removed from all products.

Laxatives, anti-diarrheals, emetics and antiemetics make up the third category of non-prescription drugs thus far subjected to an unprecedented FDA review to upgrade the safety, effectiveness and labeling accuracy of all non-prescription drug preparations.

The first monograph (antacids) is now in effect. The antimicrobial (germ-fighting) panel report is presently undergoing FDA review prior to publication of a formal regulation. Safety and effectiveness reviews also are underway and scientific reports are expected this year on the following product categories: analgesics, eye products, sleep aids, dental products, cough and cold products, contraceptives and vaginal products, and antiperspirants.

The major sub-category affected by the report being released to day is laxatives. Such products have estimated sales of some $300 million annually. The panel found that 60% of the 79 ingredients evaluated were effective, 19% needed further study, and 21% were judged ineffective or unsafe.

The panel also reported, "there is widespread misuse of self-prescribed laxatives."

"Prolonged laxative use", said the experts, "can in some instances impair normal bowel function. Use of laxatives for acute abdominal pain, vomiting, and other digestive tract symptoms can lead to serious life threatening situations.

"There are only a few valid indications for the use of laxatives; the best treatment for simple constipation should include proper diet, adequate fluid intake, and the prompt response to the urge to evacuate the bowels."

The panel suggested a number of labeling changes for laxative products, including new warnings and more detailed indications for use. Panel labeling recommendations include:

Statements of indications for use should be specific and confined to the conditions for which the product is recommended.

Effectiveness must be defined without vague or unsupported claims. Promises of general benefits in good health or well being or warnings against the hazards of constipation are unacceptable as are undocumented claims that laxatives relieve "indigestion," "excessive belching," "after-meal discomfort," "headaches," or "biliousness."

Any statement that suggests a laxative is somehow "natural" is misleading. "It is not considered 'natural' to take any laxative," said the experts.

Warnings should include: "Do not use when abdominal pain, nausea, or vomiting are present." Frequent or prolonged use in the case of some laxatives may result in dependence on laxatives.

The panel also concluded that laxative labels should contain a warning of the possibility of cancer such as, "If you have noticed a sudden change in bowel habits lasting for more than two weeks, consult a physician before using a laxative."

And, "No laxative should be used longer than one week except under the advice and supervision of a physician. . . ."

Two long-familiar ingredients—castor oil and mineral oil—are singled out for special warnings. The panel recommended castor oil be taken infrequently and then only as a one time, single dose. Mineral oil preparations would be required to have a warning against use at the same time with other laxatives and with certain other drugs as well as a requirement that plain mineral oil (unemulsified) be taken only at bedtime and then only by certain individuals.

Anti-diarrheals was the second sub-category of products evaluated by the panel. Of the 22 ingredients evaluated, four were judged effective, including opium powder, tincture of opium and paregoric. The fourth ingredient, polycarbophil, is a chemical approved by FDA for both laxative use and treatment of diarrhea. Polycarbophil is the only non-opium derived ingredient judged by the panel to be fully effective for diarrhea.

More than half of the 22 anti-diarrheal ingredients evaluated were judged to need further clinical studies to confirm manufacturers' claims. These ingredients include kaolin, pectin and bismuth subsalicylate.

For the third sub-category of products studied, antiemetics, three of eight ingredients evaluated were rated effective for relief of motion sickness. The panel recommended that specific warnings should be required on all anti-emetics to alert users to the possibility of side effects ranging from reduced bowel function to aggravation of prostrate trouble to glaucoma.

Only one emetic ingredient, ipecac syrup, was evaluated by the panel. It was judged effective.

Interested persons may comment in writing within 120 days on the proposal which will appear in the Federal Register of March 21, 1975. All comments should be sent to the Office of the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Maryland 20852.

OTC Laxative Panel Press Conference

ALEXANDER M. SCHMIDT, M.D., COMMISSIONER OF FOODS AND DRUGS, MARCH 20, 1975

We have invited you here today for two reasons:

First, to bring you up-to-date on the Food and Drug Administration's program to assure consumers that all non-prescription drugs are effective as well as safe. As you know, this is an ambitious project and one that has never been done before—at least as far as effectiveness is concerned.

Second—and as an integral part of the total drug review—we will report the conclusions and recommendations of an expert committee which has just spent 22 months evaluating more than 100 active ingredients now used in laxatives, antidiarrheals, emetics, and antiemetic drugs. These four types of products constitute one of the 27 basic non-prescription product categories that we have established in order to make manageable the massive problem of assuring the safety and effectiveness of many thousands of individual preparations.

Before we discuss this specific report, let me briefly tell you where we are with the overall review program.

It is now three years since FDA initiated what undoubtedly is one of the most complex—and most important—consumer protection efforts ever attempted by the Agency.

The Non-Prescription Drug Review was started and is being carried out within our clear commitment to the concept of self-medication. Our goal is to assure that all drugs sold over-the-counter for use without physician supervision are safe and effective, and that their labeling is clear, complete and truthful.

Our goal is easy to articulate. Building a practical vehicle for moving us toward that goal was not so easy. It is made difficult by sheer numbers. Based on whose "guesstimate" you accept, there are between 160,000 and 500,000 individual non-prescription drug products now marketed in this country. It is simply not possible—either scientifically or logistically—to evaluate this mass of non-prescription products item-by-item as we have already done with the few thousand prescription drugs.

So, we are pursuing our goal of safe and effective non-prescription drugs through the use of 17 expert, scientific advisory panels, each charged with evaluating ingredients, dosages, and labeling for an entire class or category of non-prescription drugs.

Each panel is developing a monograph—a kind of recipe book—for its assigned product category. The idea is that any manufacturer using ingredients, dosages, formulations and labeling as specified in the monograph can market its products without FDA pre-clearance. Any product not in conformance with the monograph for that class of drugs requires FDA pre-clearance via a New Drug Application.

As I have said, we decided on 27 basic categories for review, but 17 expert panels to conduct the review. We have fewer committees than categories because some of the categories such as laxatives and antidiarrheals are so closely related that they can be combined for review by a single committee.

Three of the 17 panels have now completed their work. The first panel evaluated the antacids and a final regulatory monograph has been issued. Antacid manufacturers are now adhering to the FDA monograph for this class of non-prescription preparations. You can now see the results of this work in the composition of the products, on their labels and in their advertising.

The number two panel was concerned with antimicrobials—the germ fighting agents used in deodorant soaps and other such products. This report was published for comment on September 13, 1974, and the FDA is now evaluating the public response. We expect to issue a final monograph during early 1976.

The third panel to complete its work is the one we will hear from today.

Of the remaining 14 panels, we expect half to complete their reports before the end of this year. Included are panels on analgesics, eye products, sleep aids, dental products, cough and cold products, contraceptive and vaginal products, and antiperspirants. The remaining seven review committees are all in existence and actively reviewing data.

Based on our experience to this time, we can now report with confidence—and some gratification—that the program is working. We now know that the ambitious goal we set for ourselves in the beginning is not beyond our reach.

The "category" approach to OTC drugs is appropriate and workable. Even if it were feasible, we now know it is not necessary to evaluate hundreds of thousands of individual products one-by-one to assure the American public that the non-prescription drugs they buy are safe and effective and properly labeled.

The review process we have built provides flexibility that both industry and the FDA can use to react quickly whenever a serious problem is identified. Perhaps the best example thus far is the 1972 ban on hexachlorophene in non-prescription preparations. The action was undertaken by FDA with data evaluation provided by the OTC panel on antimicrobials.

And the flexibility doesn't work just for negative action. It also works positively to allow manufacturers a reasonable opportunity to prove the value of ingredients which they want to keep but which require further testing to demonstrate that they are safe and effective.

It is now clear that the review will not force hundreds or thousands of "old favorites" off the market as some had feared.

Many products will have to make labeling and/or formulation changes, some of them extensive. Many such changes already have been made voluntarily by an alert industry anticipating the outcome of the expert review.

But necessary product changes *can* be made and, indeed, are now being made without altering the appearance or taste of popular remedies at the same time the changes are assuring effectiveness or safety and the ability of the consumer to use these remedies properly. Thus, the process is working, and working well.

Certainly, no other FDA program has been more demanding in its scientific, legal and organizational requirements. But few regulatory programs in FDA's history are likely to have greater positive impact on individual consumers.

In overcoming these difficulties and in achieving this impact, we are, I believe, taking an unprecedented forward step toward improved health protection for the American public.

This ends my general statement. I would now turn your attention to the specific report before you. In doing so, I will offer this three-point preamble:

First, the report is an advisory report to the FDA Commissioner. It was prepared by the best qualified scientists we could find. Beginning with this press conference, we will spread this report on the public record in a search for consumer, professional and industry reaction. Only after we have this further advice and comment will the Agency complete its own evaluation and attempt to write a final regulation.

Second, the report we release today is a review and evaluation of ingredients and of ingredient uses in non-prescription laxatives, anti-diarrheals, emetics and antiemetics. It is not a review of individual, or brand named products. Each ingredient under review has been rated by the panel in category I, safe and effective; or category II unsafe or ineffective; or category III, safety and effectiveness not adequately demonstrated by existing data. Category I ingredients can be used as described in the monograph; category III ingredients can be used for a set period of time if experimental work to prove safety and/or efficacy is undertaken; category II ingredients will come out of the drugs.

Third, and finally, this report, like those still to come, contains negative findings. As you will see in our press release, about 20% of more than 100 ingredients evaluated are, in the judgment of this advisory panel, unsafe or ineffective for the claimed use. But the percentage of good to bad ingredients in this report does not extrapolate to the percentage of good and bad products now on the market.

For example, calomel, a mercury-based ingredient, is among the 20% of ingredients judged by the expert panel to be unsafe. But calomel is highly unlikely to be found today in any but a very few laxative preparations.

If you keep the negatives in perspective, I believe you will go out of here believing as I do that the unfolding story of the OTC review is essentially hopeful and, overall, entirely positive.

And now, it gives me considerable pleasure to present to you Dr. Nicholas Hightower. Dr. Hightower is Director of the Division of Research and Education at the Scott & White Memorial Hospital in Temple, Texas. He is Chairman of FDA's Laxatives, Antidiarrheals, Antiemetics and Emetics Review Committee.

Dr. Hightower will explain the findings and recommendations of this expert advisory group to the Food and Drug Administration and, then, both of us will be happy to respond to any questions you may have.

Thank you.

[FDA SUBMISSIONS FOR THE RECORD RECEIVED BY THE SUBCOMMITTEE AUGUST 13, 1975.]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
OFFICE OF THE SECRETARY,
Washington, D.C.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations and Human Resources, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: Enclosed is the edited transcript of testimony presented before your Subcommittee on May 12, 1975. Thirteen submissions for the record are included with the transcript.

In addition to the submissions specifically requested or agreed to during the hearing, we are submitting three additional ones which we respectfully request be included in the printed record of the hearing to insure that the record is complete. These are:

The nomination hearing for Peter Hutt before the Senate Committee on Commerce during the 92d Congress;

Memorandum of visit between Mr. Armond Welch, Executive Secretary, Over-the-Counter Antacid Review Panel and Mr. Gilbert S. Goldhammer;

Copies of one page from the final panel report, April 5, 1973, proposed regulation, the tentative final order and the final order.

In addition, a letter from the Commissioner of Food and Drugs to you regarding the discussion on pages 108 and 109 of the transcript will issue shortly.

I apologize for the delay in submitting this material.

Sincerely yours,

DALE W. SOPPER,
Acting Assistant Secretary for Legislation (Health).

EDITED TRANSCRIPT OF REMARKS BY PETER BARTON HUTT, ESQ., ASSISTANT GENERAL COUNSEL, FOOD AND DRUG DIVISION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, JULY 26, 1974

Subjects covered in the Remarks include: the historical development of the Review; the roles of the Consumer and Industry Liaison; that part of FDA's May 11, 1972 Procedural Regulations for Classification of Over-the-Counter Drugs dealing with standards for safety, effectiveness, and labeling; confidentiality of the material submitted to the Panel; the importance FDA has placed on the Review; as well as a general history of the development of the Food, Drug, and Cosmetic Act.

[Mr. Hutt's remarks were made from notes and are not to be considered as a formal presentation. They have been transcribed from tapes and certain editing has been done by The Proprietary Association staff for clarity and readability. Emphasis has been supplied to focus attention on major points.][1]

What I will try to do is fill in a little bit of the history, taking up some of the points that I'm sure Carl [Mr. Carl M. Leventhal, M.D., Deputy Director, Bureau of Drugs] has covered but I will do even worse than he and go back to 1906 and come forward with some of the relevant background. [This is] because I think it's terribly important that you understand how what you are doing fits, not just into the OTC Review and indeed not just into the whole effectiveness of drugs review that the FDA has been undertaking since 1962, but indeed into the whole statutory framework of the Food and Drug Act and into, you might say, the Food and Drug Administration history. I would urge you, and I mean this, to please interrupt me at any time where I'm getting into an area that I'm not explaining well enough or where you have some questions—and that includes any of the people who are not members of the Panel but who are sitting around the room as well.

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[1] Page bears statement at bottom: "The Proprietary Association—9/5/74—gK."

The 1906 Act, where I always begin, was the product of a great deal of work—largely by one individual in the United States Department of Agriculture who was concerned at that time with the sanitation of food. His name, as you may know, was Harvey W. Wiley. Dr. Wiley was not terribly interested or concerned, interestingly, with the safety and effectiveness of drugs. Earlier in 1902, there had been a biologic statute enacted by Congress which, interestingly, survives to this day and it is the basis for the work of our Bureau of Biologics, formerly the Division of Biological Standards in the National Institutes of Health, but that's an entire other area.

The 1906 Act did contain basic—what I now call rather primitive—provisions that outlawed any adulteration or misbranding of drugs; but it did not go into the enormous detail that the 1938 or 1952 laws did as to what constituted adulteration or misbranding. It was, in short, the kind of legislation—the primitive beginnings of a Food and Drug law—which perhaps was sufficient for 1906 up to the 1930's, but would not be sufficient today in light of our more sophisticated forms of medication.

Now, in 1933, Congress realized, and President Roosevelt realized, that the 1906 Act simply was not sufficient. So legislation was introduced within the first 100 days under President Roosevelt to revise the 1906 Act. It was the so-called Tugwell Bill because Rexford Tugwell [then Assistant Secretary of Agriculture], along with a few law school professors, put the thing together. It took from 1933 to 1938 for that piece of legislation to be perfected and ultimately to be enacted by Congress.

Interestingly, one of the major issues at that time is an issue that still is with us today, but it held up that legislation, probably for three of the five years. That was that the original bill would have given the role of advertising of over-the-counter—indeed all drugs and foods, cosmetics and devices—to the Food and Drug Administration rather than to the Federal Trade Commission. That was an absolutely bloodly battle in Congress at that time that resulted in the 1938 Wheeler-Lea Amendments to the FTC Act which gave the FTC jurisdiction over advertising of foods, drugs, cosmetics, etc., and gave the Food and Drug Administration jurisdiction over labeling.

Now before that troubles you very much, let me assure you that we still have a hook on advertising and FTC has a complete hook on labeling. So we work closely together and usually work these matters out. That famous jurisdictional dispute has never really amounted to very much in terms of actual practice.

In late 1937, as the legislation was mostly complete—in fact, it was entirely complete at that time and ready for enactment—the famous elixir of sulfanilamide disaster occurred. Some of you may know of that. Let me just briefly describe it.

Massengill wanted to put out the first elixir of sulfa rather than just tablets or powdered form or whatever it used to put out before. They needed a good solvent, and so they found one—we call it antifreeze today. The difficulty was that they either killed or blinded over a hundred people within a couple of weeks before people discovered what it was and got it off the market.

Well, the net result was that Congress tacked onto the pending legislation what we now call the New Drug Provisions of the law. The New Drug Provisions define a new drug as any drug that is not generally recognized as safe. At least, that was the 1938 definition. It was changed in 1962 to add effectiveness as Carl has mentioned. And the New Drug Provisions say that any new drug cannot be marketed until a New Drug Application has been submitted to the Food and Drug Administration and at that time the FDA did not veto its marketing. Today we have to approve it. And I'll get to that in a moment.

So from 1938 to 1962, FDA has had the legal requirement, for any new drug, to review an NDA and either allow the drug to be marketed or prohibit the drug from being marketed. Interestingly, if we go back and look at the 1938-1962 statistics, we find that there were 429 OTC drugs that went through the NDA process during that time. There were about 7500 prescription drugs. I would imagine—although we've never gotten the actual statistics—if we were to factor out the number of prescription drugs marketed between '38 and '62 and compare it with the number of OTC drugs marketed, you would find just the reverse. There were probably a couple hundred thousand OTC drugs and maybe 20, 30, or 60 thousand prescription drugs. So what this meant was that virtually all the NDA's were submitted on prescription drugs. A minuscule portion of the OTC market was subject to an NDA. This became quite relevant when, in 1962, our second national drug disaster, thalidomide, occurred. Congress again took a bill that was absolutely dead—the Drug Amendments of '62 (I remember because I

was in private practice at the time). In June of '62 the drug amendments were officially buried. Congress decided not to act; it wasn't an important problem and the issue was gone, and the pharmaceutical industry went off to worry about other things.

Then on July 15, 1962 Morton Mintz wrote a now-famous front-page story in the Washington Post, which for the first time broke the thalidomide story on a public basis—the scientific community had known about it for some weeks and months. The result was that on October 10, 1962 that bill was passed in both Houses and signed by the President—a bill that was otherwise absolutely gone. So that was a rather interesting period of time.

In any event, that bill expanded the definition of new drug to include effectiveness; it required FDA not only to permit a new drug to be marketed, but to indeed approve it affirmatively as safe and effective. Also, it required FDA to go back and review every drug, which had been previously subject to an NDA, for effectiveness. Obviously those drugs had been reviewed for safety between '38 and '62, but the law said to go back and review all those drugs for effectiveness.

Well, we started out with the prescription drugs, as Carl has mentioned, and that, I might add, is still in the process of being implemented and there are those of us that disparage Carl of that effort being fully completed. I think Carl is beginning to learn the difficulties, coming just recently from NIH himself.

Starting in 1966 (I wasn't here for all of Carl's presentation but he may have mentioned) we went to the National Academy of Sciences (NAS), and in hindsight we now realize there were three problems created by the way we did that operation. The first problem was that the NAS Committees met behind closed doors. Not only was there no consumer and no industry person who ever met with one of those committees—there was no Food and Drug Administration employee who ever, on one occasion, attended one of those meetings. If ever there was an ivory tower type situation, that was it. There was no interplay, no discussion, no submission of documents, no questions asked, no nothing. That was the first problem. And as I say, we learn from our past mistakes. At this point I always say, Wally [Wallace L. Guess, Ph. D., Panel Chairman], that I'm sure that ten years from now, someone will be sitting in this room saying, "That fool Hutt, if he had only thought of this. And what was Charlie Edwards doing when he did it this way, he should have done it that way." We're all going to go through that. And I'm sure that there will inevitably evolve improvements on our present process. But what we're doing is improving the past process.

The second problem was that the report that was issued was, I don't think, in any case, over one page long. (Don't you wish you could go back to those days, Wally?) [comment from Wally] It was simply a summary that the committee, having reviewed all the pertinent scientific data and evidence, concludes *that:*—and came to whatever it concluded. Well, when it came time to enforce that in the courts, I found, and my predecessor, Bill Goodrich, found it somewhat difficult to explain to a judge why it was that we should take a drug off the market that was used by every physician in the country for forty years and had 30 million dollars worth of sales a year on the basis of just one sentence in a scientific report when noone had an opportunity to interrupt the panel meeting. So we concluded that whatever was done had to be justified in what I call exquisite detail, which is what this report [i.e. Antimicrobial I] does, very, very superbly. It's going to be one of the real fine reports that comes out of this or any type of preceeding of this nature.

And then there was a third problem, and that was that the way the NAS approach worked—they did it drug by drug. Now I mentioned that there were some 7500 or 8000 drugs. By the time they weeded out the ones that were no longer marketed or that were identical to other drugs, really, it was down to about 4000. But that meant we received 4000 reports. Although a major amount of them came on one day, the fact remains that you cannot implement 4000 reports all on the same day. You can't put all of those in the Federal Register or the National Archives [and Records Service], who don't like us as it is. They would really go berserk on that one. So what it meant was that competitive inequities inevitably resulted. We would deal with one antibiotic first and then maybe six or eight months later, or two years later, get around to a competing antibotic. This meant that there was an enormous confusion in the outside world, both in the industry and, I think, in the medical profession. They couldn't understand why we couldn't do everything at once. Those of you who've worked in government or indeed, I think, had any contact realize that it takes a while for the regulatory procedure or mechanism to work. So the competitive inequities worried us tremendously, and we decided with the OTC Review, quite obviously, to deal with drugs on a class basis so that we are dealing with all antimicrobials, all antacids,

all analgesics, etc., and would not get into this situation—forcing one person to relabel or reformulate before another, etc.

Well, the original NAS Review did include these 420 over-the-counter drugs, but it was obvious, when we got down to those, in terms of implementation, that the amount of scientific data and information that they received on those was minuscule compared to what was out there. And while those 420 drugs might be—in a narrow sense—representative of the 200,000 that were out there, i.e. representative in the sense that there might be one of each type, they weren't representative in terms of all the ingredients, all of the labeling issues, all of the safety problems.

Now the approach that was adopted is in your folders. It's the May 11, 1972 OTC Regs. Let me explain, since none of you are terribly familiar with the regulatory process, how a regulatory agency works when it goes about this kind of thing, because there are some legal strictures that must be followed.

When we establish regulations, the law requires, for I think eminently sound reasons, that we first publish a proposal in the Federal Register and give any interested member of the public—the academic world, the man on the street, the industry, anybody else—the opportunity to write us and either say that's a good idea or, my gosh, you're a bunch of fools in Washington, why don't you do it some other way. We then, on the basis of those comments, publish a final regulation which contains a preamble, as we call it, that lays out all the comments, and what our answer or resolution is for those comments. So if someone writes in and says, "You have defined safety in the following way. I think that you haven't taken account of this factor . . .", we will say in the preamble, "one comment questioned the safety on the grounds that . . ." And then the Commissioner concludes that either his comments should be accepted or rejected, and says why. Now we try not to write textbooks, although sometimes our preambles look like textbooks. This happens to be one of the longer ones. But the concept is to make it clear that we *do* read the comments, we *do* take them into consideration and that the final regulation has a clear rationale behind it.

It was on January 5, 1972 that we proposed our regulation. We received a great number of comments and on May 11, 1972 we published this final regulation which is before you. Now the first 14 pages of that regulation constitute the preamble. It consists of 98 numbered paragraphs. The next four pages constitute the actual regulation itself. I would urge you, as I have urged every Panel, to first read the preamble to get an idea of what was involved in the entire thing. Then read the barebones regulation itself and then after having read that, go back and read the preamble again. I think that if you just read the regulation you will not get all the color and flavor and atmosphere and intended meaning out of it. I think, Wally, you might agree, after having wrestled with it for almost two years, that statutory language that lawyers, like myself, write in regulations isn't always, to the average scientist or layman, the most informative. And that is why the narrative in the preamble may be very helpful in terms of explaining it in terms of greater length and in greater depth. I will come back to various parts of that preamble, but I want to pick up on some of Carl's remarks about the concept of having a panel.

To my way of thinking—Carl looks at this from a scientific standpoint. Obviously, from a scientific standpoint, a panel is the most intelligent way to gather different points of view, to gather the best expertise in the country on the subject, which you people represent, and to put it together into something that makes good, sound, scientific sense. From a legal and regulatory standpoint, I feel, if anything, even stronger about that because it's clear that when you regulate in a scientific area you're always on thin ice. There's no such thing as scientific certainty, and accordingly, when you're in the area of regulations in science, there's no such thing as absolute regulatory certainty. What we need is a consensus of the best judgment at the time—something that I can go to the courts and say is eminently reasonable—not arbitrary or capricious, which are statutory terms of things that we can't do. We can be arbitrary *or* capricious, but we can't be both, according to the law.

In any event, I have found—for example, even with the drawbacks that were inherent in the way the NAS went about its method of review—that the courts were terribly impressed with the fact that we did go to the nation's leading scientists, rather than just sitting in our own halls and listening to our own employees—that we went outside and got the best independent judgment that we could. And as a result, the courts have uniformly upheld decisions emanating out of the basic DESI prescription drug review. So from a regulatory standpoint, I think the use of outside advisors is probably one of the best things the Agency has ever done.

Now, I would say, and I've emphasized this to every Panel, Wally, as you know, that we are not interested in outside people coming in and rubber-stamping what the Agency thinks is right or wrong. That is not the purpose. If we'd wanted to do that, it would have been very simple. We wouldn't have had any outside experts. What we want you to do is to take a totally fresh, independent, objective—to the extent that these things can be objective—view of this entire field, come up with your best advice and give it to us. Now that includes, I might add, things that we perhaps have not even asked you to look at. Some Panels have looked at issues, such as whether the pharmacist ought to be on the label or shouldn't be on the label, which created a huge flack; such as whether cosmetics should be regulated in a certain way or not. That isn't actually an over-the-counter drug issue, but we've said, "That's fine—give us your advice on it." We want it and we'll find a way to implement it.

Issues have arisen whether the percent or the quantity of an over-the-counter drug's active ingredient should be on the label. The statute says we can't require it on the label. I don't care what the statute says. If you think it ought to be on the label, if you want to put it in your report, please put it in your report. In short, don't feel constrained by some kind of legal boundaries that you believe may exist or that I may have to tell you exist. We want your advice. We may have to come back later and say, "I'm sorry, we can't do that one, but we'll do everything but that." Maybe we'll have to go to Congress and say, "We have had a lot of advice to get the percent of the active ingredient on the label, you're going to have to change the law." But those are things that I don't think you should concern yourselves with. You should concern yourselves with the scientific and the medical issues that underlie this review, and I can't over-emphasize that.

Time and again I've gone back to Panels and said, "Look—don't worry about the law. That's my problem. I've got the responsibility for implementing what you want to do, and one way or another I'm quite confident that we will find a way to implement it." So you just go ahead with what makes good sound scientific and medical sense. I think that our last Panel, the Antimicrobial I Panel, has done that with eminent success. It has not felt constrained at all by views of the law. It has recommended that we go ahead and, for example, exert the same controls over cosmetics as over drugs. And we have a system all prepared to do that; so I'm sure that this Panel will meet some of the same issues, and Wally, I would say the same thing to you I've said for two years on that count.

One other thing I would also mention from a legal standpoint, in terms of the use of advisory committees or panels of this type. A year ago, in June of 1973, the Supreme Court handed down four decisions dealing with our authority over new drugs and these are the only decisions that have reached the level of the Supreme Court in the new drug area. In all four of those decisions the Court did emphasize that FDA has what lawyers call "primary jurisdiction" in the area of the regulation of over-the-counter and prescription drugs. "Primary jurisdiction," in lay language, means that the courts will defer to our decisions as long as they are reasonable. And indeed, if issues of this kind are presented to the courts, they will decline to take action until the Agency has looked at the issue and has given its advice. In short, it places the Agency in a very strong and powerful position in terms of regulatory control. Now that's very nice when you're a regulatory official to be in that position because it allows you to do many things that otherwise, perhaps, you couldn't. But, that's just one side of the coin, as I constantly emphasize.

The other side of the coin is that it imposes on us an absolute obligation to make sure that when we do issue our regulations that they represent the best scientific and medical advice in the country. A regulatory agency with primary jurisdiction should not simply sit there and hold all of its decisions close to its own vest. It ought to go out and consult the country—and I mean that truly—consult the country in terms of industry, in terms of consumers, and in terms of the scientific medical expertise before it makes those decisions. And that, again, is something that we have been trying to do in which you represent one part of the process.

Let me then turn for a moment to the use of the industry and consumer liaison members. I'm sure that Bob Pinco [i.e. Robert Pinco, Esq., R.Ph., FDA OTC Drug Products Evaluation Staff] will get into this at greater length, but I would like to refer to it. This was a complete innovation back in January of 1972. We had never before, in use of advisory committees, consciously gone out and chosen an industry liaison and consumer liaison in order to inject into the decisional process, at the earliest stages of the game, the viewpoints of both of those groups. Again, it arose in part because of our concern over the lack of this type of input in the National Academy of Sciences review of prescription drugs. We're fortunate

in this Panel because we have survivors from the last Panel in that they understand how well this process has worked. I think it is absolutely clear that no Panels in the entire OTC Review could have done as good a job if they had not had immediate access to the kind of scientific data that often resides in the industry files and which can be made available on 30-days notice, which is basically what it has been for the Panels in the past, and I'm sure it will be to this one.

Everybody comes to a meeting like this with preconceived ideas of what the real issues are, and I think those who have gone through the process for two years will tell you that some of those ideas change radically in the course of the discussion. Issues that you think exist may be disposed of in a day. Issues which you aren't aware of may take more than a year. When those new issues crop up, quite frequently you're going to take advantage of Carl's offer to go and get outside experts from around the world to come in and give you the benefit of their advice and their experience. You're also going to want to go to industry, through the Liaison, to get all the published and unpublished data on that particular issue that can be brought to bear on the problem in a very immediate and responsive way.

It starts at the top of Page 16 of the copy that you have. You will see in the left hand column, a series of definitions: (1) safety; (2) effectiveness; (3) the benefit-to-risk ratio; (4) the combination policy; (5) labeling; and (6) the statement of when drugs will be OTC as contrasted with prescription. Let me turn first to safety.

I'm always amused to admit that no law ever enacted by Congress has definitively defined the concept of safety. In fact, the closest that the Congress has come was in 1938 when it said that for a new drug, safety must be shown by all tests reasonably applicable to show safety. I somehow find my scientific colleagues are still wandering through that thicket. They don't think it terribly helpful. I, of course, as a lawyer, think it's superb because it doesn't say anything and it allows me to argue anything. It is, obviously a circular definition, and although we have tried to improve upon it, I'm not entirely certain that our definition is any more explicit or terribly helpful in the deliberations at hand.

PANEL MEMBER. The psychologists' favorite example is that intelligence quotient is what an IQ test measures.

Mr. HUTT. That's about the size of it. We say that safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. I was always very proud of that method as a matter of fact. It says something. I'm not entirely certain what, but it is an attempt to put down some concepts. I think, in all seriousness, it's quite clear that we could not write a definition that would be overly helpful to you. In the last analysis, the judgment on safety is a judgment. It is a judgment of experts who are qualified to analyze toxicological and pharmacological data and to balance benefit and risk and make judgments of this type. So, certainly in the area of safety, judgment of the Panel is going to be absolutely critical and those who have gone through the process, I think, will agree. Do you want to dispute that?

PANEL MEMBER. Over a several-hour period, we discussed the term "relative safety," but what did we finally come up with? "Significant safety?"

Mr. HUTT. Well, I think it's clear that safety has always been interpreted to include benefit-risk. Once you include benefit-risk, you are talking about "relative safety" or "significant safety" or any other choice of words that you may come up with.

The same thing is true and has been true of the consumer representative. It certainly occurred to us from the beginning that for a bunch of doctors, toxicologists, and pharmacologists to sit around and decide what labeling means, wasn't really a complete picture. What you needed were a few consumers who represent organizations that deal with these kinds of issues on a daily basis. Moreover, for a group of experts to sit around and talk about what consumers are worried about, in the field of OTC medication, is incomplete. You, I don't think, have as good a feeling about what the average person on the street is using these drugs for, and what the average person is concerned about in their safety and effectiveness, as does the Consumers Union and the Consumer Federation of America and various other consumer groups. I get hundreds and hundreds of letters on the subject all the time. So we feel that this great experiment that started out in 1972 has turned out to be one of the best things that we have come up with in the way of bringing the entire public into a decisional process.

Now, we shied away, and continue to shy away, from having totally open meetings in which any member of the industry and public could come, for one very simple reason. We want to retain the freedom of discussions that can go with a group of people coming to know each other and respect each other and trust each other. People obviously say things in closed meetings that they are not willing to say if they know it is going to appear in the newspapers the next morning. I'm sure that all of you are willing to criticize your colleagues' work on a scientific level, but you hesitate to do so if it sounds like you're being highly critical of the individual as an individual.

We've had many instances where people have hesitated to express opinions on brand names of products in the marketplace or to discuss them in an open forum—where they would be quite willing to do so in a closed forum. Again, we have had instances where the stock market has gone up or down 30 points because of rumors of how the OTC Review was handling a given problem. Those kinds of issues do concern us and for that reason we have held the discussions in closed sessions, although we have, in most instances, provided that the minutes of a meeting may be released at the Panel's discretion on a current basis rather than waiting until the end of the process.

I think that I need not go on more about the liaison members except to say that we are very, very much committed to the use of this process and it has worked out terribly well.

A word now, in returning to regulations, about some of the definitions under which you will be operating. The reason for regulations is to make certain that all of the 17 diverse Panels—which have 7 times 17 members (whatever that turns out to be)—use the same fundamental concepts when they refer to safety, to effectiveness, to combination drugs, benefit-risk ratios, to appropriate labeling. We defined those terms and concepts in the Federal Register and I would like to run over them with you for just a moment because they are the critical definitions.

Well, that is the first definition. Now the second definition, on its face, is a good deal more definitive, but when you go behind it I think it probably involves as much judgment. In 1962 Congress did define effectiveness. Congress said that effectiveness is to be determined by adequate and well-controlled clinical investigations. Now obviously, at the same time, we know that not every drug is susceptible to an adequate and well-controlled clinical study. My favorite, of course, is snake bite remedy. I wouldn't mind if someone else were on the placebo, but I wouldn't want to be. There are other drugs where it simply doesn't make sense to run an adequate and well-controlled clinical study. And I might add—I will not fall into the trap of describing which ones those are because that's up to the Panel. And here again I get to the point of judgment. We provide in here [May 11, 1972 OTC Review Regulations, 37 Federal Register at 9474] that effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions and warnings, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in our regulations, unless—here's the "unless" clause and where the "judgment" clearly enters in—this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness.

Now what this means is that we recognize that there are some over-the-counter medications, in particular, where it simply would not make sense to go back on a product that's been on the market for a hundred years and is absolutely recognized by everyone as effective—and run an adequate and well-controlled clinical study. In other instances it will make sense to require that. And the judgment as to when that is and is not scientifically defensible or indefensible, obviously, resides in the Panel. Once again I have a definition that I was able to devise which throws the ball back in your court and allows me to escape all the decisions.

The third point is that—I think it is obvious but we decided to put it in the regulations anyway—the benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness.

The combination drug policy probably has resulted in greater discussion and controversy than any other part of the OTC Drug Review. I think that's safe to say and in every Panel it will remain that way. You obviously have two problems. You have a problem where you have two ingredients with the same effect, e.g., two antacids, and the product remains simply an antacid. Then you have the problem where you have two ingredients for different effects, e.g., the Alka-seltzer problem, as I call it, where you have an antacid and an analgesic, which,

as you may be aware, resulted in a small amount of controversy as well as two Congressional hearings, and which we may still have controversy on in the future. So, what we try to do is put it in the simplest of lay terms. I say that because I was the simple lay person who defined this—and try not to get into complex scientific discussions in terms of combination drugs. We laid it out in terms of three requirements and they are set out here. I will simply read them one at a time and describe to you my understanding of it.

The first is that a drug may be combined with another when each active ingredient makes a contribution to the claimed effect(s). Now, let me stop here and give you my understanding of that. It seems to me, just eminently common lay sense, that if you have two ingredients in a drug and one doesn't do anything, that one shouldn't be there. It has never seemed to me terribly controversial to take that position. Now, if, for example—let me use antacids since the Antacid Report is now final and it provides some good examples of this—you have a drug product, an antacid, and it contains three antacid ingredients, each one of which, let's say, is a perfectly safe ingredient but one of them contributes absolutely nothing and each of the other two contribute 50 percent of the total activity of the product, the easy answer is to take out that one antacid (non-antacid) ingredient. If it were on the label it would be a fraud because it isn't doing anything. It isn't an active ingredient and there is always some risk that if a drug ingredient doesn't do anything, it could have adverse reactions. So, from a benefit-risk standpoint, there's no benefit. There's a possibility of risk and there's no justification for that ingredient whatever. I think in general terms that that proposition has been fairly widely accepted.

One issue that arises—I don't know to what extent it will arise with this particular Panel—is how many ingredients with the same effect you can have. Now the Antacid Panel said as long as it contributes 25 percent of the activity of the product, that is sufficient to call it an active ingredient. That is not a magical number. You can look at that issue in any number of different ways. Some other Panels have said that no more than one ingredient is justified because in those other Panels they were dealing with ingredients, that if you add two, you would increase the risk without increasing the benefit and therefore it's unjustified. This is an area that I'm sure you'll spend an enormous amount of time discussing. So much for the first criterion.

The second is: when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients. Now let me, then, describe what the tint of this was. If you put two ingredients together, "A" and "B," which are ordinarily effective or safe by themselves, but they combine in a way that ingredient "A" binds up ingredient "B" and makes it ineffective, then obviously that combination doesn't make any sense. Again, I don't think this has been terribly controversial and has not created a great many problems.

Then we get to the third one which is a little more difficult: when the combination, when used under adequate directions and warnings, provides rational concurrent therapy for a significant portion of the target population. Now, what were we talking about here? We're talking about two or three things, and if I had it to do all over again maybe I would split it up and try to separate them.

First, it's quite clear that since we have 200 million people in this country, any individual at any one time may appropriately be taking a combination of active ingredients. That doesn't mean that any combination of any active ingredients makes rational concurrent therapy for a target population. Because if the target population is only one person in the entire United States, it just doesn't make sense. What we are talking about is: first it has to be a significant target population. The Antacid Panel concluded that—just to give one example and go back to my antacid/analgesic example—there *were* a substantial number of people who take both an antacid and an analgesic at the same time and therefore, combining those was rational. They also concluded that there was not a substantial target population who would take a laxative and an antacid at the same time and they said that made no sense, whatever. Not being medically or, scientifically trained I cannot debate whether they were right or wrong on those but that does at least illustrate the problem. That is part of it.

The second is that the concurrent therapy has to be rational in the sense that you can't have two active ingredients that sort of counteract each other. You have to have active ingredients that work together and that one would conclude should be taken together from a medical and scientific standpoint. And this probably has more judgment built into it, this part of the combination policy, than any other part that we deal with and I am sure that you will find a good

amount of time will be spent just debating what these words actually mean and how they should be applied in individual situations.

PANEL MEMBER. Before you leave that particular topic, as you remember, one of the stickiest parts of our [i.e. Antimicrobial I] combination policy was: does each one have to make a significant contribution to the total effect synergistically?

Mr. HUTT. The issue is usually phrased: "Must there be an additional benefit? Must there be an increase in safety or an increase in effectiveness?" The answer, which we have said flatly at the beginning of this, is NO. There is no requirement that it be safer or more effective as long as it is as safe and as effective as the individual components. Now, let me contrast two things because this constantly arises and I spent one morning with Antimicrobial I on this. Let's contrast antibiotics with antacids. When you combine four different antacid active ingredients to make up a single product, there is no doubt in the Antacid Panel's mind that you are not increasing any risk at all. It's not as though you're adding new side effects every time you add a different ingredient. Accordingly, the product using four active ingredients as compared with one active ingredient is as safe and as effective and therefore is perfectly permissible.

Now, let's assume that instead of antacids we had some antibiotics because that's the one that we've litigated in the courts in the prescription area. There, if instead of having, say, one antibiotic at full strength, let's say you have four antibiotics each at 25 percent of strength (I may be scientifically wrong, but let's assume that proposition for the moment). What you're doing is adding—you're quadrupling the risk because each one of those antibiotics carries with it its own unique side effects and adverse reactions, etc. You're not necessarily increasing the benefits but what you have to do is look at the benefit-risk. If you're decreasing the benefit-risk ratio, then obviously it's less safe or less effective. So this becomes a very interesting analytical and intellectual area. It's an area that you [i.e. Antimicrobial I Panel] got into at great length, but there is no rule. You [i.e. Antimicrobial I Panel] wanted me to lay down a good hard and fast rule. There is no rule. You must analyze it in terms of benefit-risk ratio. Look as to whether the combination is as safe and as effective, not more safe and more effective. Have I succeeded in confusing it again? It's a difficult issue because it's very easy for me, of course, to sit here and give you the guidelines. I don't have to carry them out.

PANEL MEMBER. This kind of contradicts what you said before. I assume that you said that every time you add another ingredient you increase the risk, the potential is there.

Mr. HUTT. There is some potential, but the area of antacids, of course, is somewhat unique. If you add an ingredient that doesn't do anything then there's no benefit-risk issue because you have some risk and no benefit. I was assuming that each one of those antacids ingredients you're adding is effective or each antibiotic is effective, and therefore there is some benefit. The question is whether the risk outweighs it.

Question. But, if you add four instead of one and the four are no more effective than that one, then can one assume that you are increasing the risk; because you're adding?

Mr. HUTT. You can in some instances and can't in others. Where you're dealing with the antacids, the Panel said first, that you weren't increasing the risk, and second, that you may be decreasing the risk because you are adding each one at 25 percent of the active level. The product, with more active ingredients could be, in that one area, safer. Again, what it comes down to is that you've got to analyze each issue. You can't make a hard and fast rule. If you say that four ingredients are okay and the 25 percent level is okay for antacids and therefore it's okay for anything else, that's a non sequitur. I understand your point.

The other reason, as I mentioned, why you would not put in an inactive ingredient is because it's a fraud. If it's inactive you can't call it an active ingredient. It doesn't do anything and people shouldn't be allowed to promote a product that has an ingredient which they say is active when it isn't. It's straight misbranding. So it's a combination of both of those reasons.

Panel Member [WALLACE GUESS]. I might add too that this isn't the last time that Peter is going to be in. It's easier talking specifics than it is in generalities and Peter will be available from time to time to discuss specific problems when you get into them, for this or any of the other areas discussed.

Mr. HUTT. Yes, especially on Saturday mornings, if you have donuts—otherwise, no.

The fifth item under the definition says that labeling shall be clear and truthful in all respects and shall not be false or misleading in any particular, which sounds like God, motherhood, and country all rolled up into one. But this does emphasize that you are not just going to be looking at an ingredient and saying, "Yes, this

is safe, and yes, this effective." As you will see when you have an opportunity to work with the Antimicrobial I Panel, you're going to have to start defining what these over-the-counter drug products are, what proper labeling should say, what a warning should say, what warnings are needed, and how to convey the information that you can come up with in terms of safety and effectiveness *to* the consumer. In this respect, review of labeling claims is going to be of paramount importance. To give you an example again—in the antacid Panel, one of *the* major issues is, was, and is going to remain for some time, whether the term "upset stomach" is appropriate for antacid products. That gets into all kinds of interesting issues as to what the term "upset stomach" means, what the consumer understands it to mean and whether this scientifically and medically describes, and on the other hand, describes to a consumer, what an antacid product does. So these kinds of issues are going to be very much before you.

The final definition here defines when a drug is permitted for over-the-counter drug sale. A drug shall be permitted for OTC sale and use by the laity unless, because of it's toxicity or other potential for harmful effects or because of the method or collateral measures necessary to its use, it may safely by sold and used only under the supervision of a physician.

Now, let me go back and pick up a little bit of the legislative history back in 1933 to 1938 that I didn't get into, but perhaps I should have, chronologically.

The issue of the status of over-the-counter drugs was debated at great length by Congress in or about 1934. At that time there were some questions raised as to whether all drugs should not be on prescription and Congress flatly decided, and it is written throughout the legislative history, that there shall be over-the-counter drugs, that people have a right to self-medication and that a regulatory agency, the Food and Drug Administration, could not deny that right except where circumstances are that only a physician's supervision should be required because of toxicity or the need for diagnosis or whatever. Now, in 1951, when Congress explicity wrote a definition of prescription drugs into the Act for the first time, that was all reiterated again. Congress again made it clear that over-the-counter drugs were to remain on the market and that it was FDA's job to make sure that they were as safe and properly labeled and now effective, as they could possibly be made. But it was not our job to say that consumers did not have the right to self-diagnosis and selfmedication.

It's difficult, at times, to draw a hard and fast line between a prescription drug and an over-the-counter drug. That is why we give you that job rather than trying to do it just by ourselves. In all seriousness, what we are asking this Panel to do, and other Panels to do, is not just simply to look at the over-the-counter drugs on the market right now and to deal with that, but to look at current existing prescription products and make a determination whether they should be considered for switching to over-the-counter products and available for self-medication, rather than keeping them on prescription. I might say the opposite is also true. If there are over-the-counter drugs today that you think should be switched to prescription, then we want you to give us that advice also. This is an area that is fully within your review and we hope that you will look at it very closely.

I almost regret making that statement. I'm reminded when I talked to the over-the-counter drug Panel dealing with vaginal-area products—contraceptive type products, etc.,—Betty Connell [Elizabeth B. Connell, M.D.], the Chairman of the Panel, asked me, "Is it within our authority to recommend that "the Pill" be put over the counter?" I said, "Yes, but I hope you think carefully before making that recommendation." That's just simply an illustration. We want these issues looked at in a completely independent and fresh viewpoint, as I said, and there is absolutely nothing that's beyond the possibility of your looking at it.

PANEL MEMBER. I think that this Panel in particular is going to be asked to look at the antibiotic prescription labels very carefully.

Mr. HUTT. And what that will mean is that you may wish to recommend to us that we draw a new line between prescription and OTC antibiotics, either in terms of dosage levels or in terms of labeling indications, or whatever. If you want to do that, that is fully within your purview. Indeed, I remember, in dealing with cough/cold products, that the Panel had an enormously difficult time. They had good evidence of effectiveness at the prescription level, and for the same ingredient, used at one-half or one-third of the level, the evidence of the effectiveness was equivocal. They must have spent two or three sessions trying to figure out how to do this. I came down and discussed it with them and said that there was no difficulty switching those prescription products to OTC and getting rid of the old one-third to one-half level and it solved the whole problem. I don't know how you're going to solve your problems. Any of these approaches is totally out in the open and whatever makes sense is obviously the way we ought to go.

What the ultimate objective of the study is—in fact I usually start a discussion this way, nasty right from the beginning, but I decided to save it for toward the end, and I always have to be terribly frank about this—the objective of what we are doing here, what you are doing here in this Panel, is different from any other study panel that you have ever worked with because what we are dealing with here is a regulatory statute. That is the fundamental importance of this exercise. It will determine what drugs stay on the market, how they are formulated and how they are labeled. It will determine that everything else, ultimately, if it can't be shown to be safe and effective, will be taken off. This is why this is so fundamentally different. I know Wally and the Antimicrobial I Panel came to feel this way, because this will be one of the most important bits of work for the government or any other organization that any of you will ever undertake. Certainly that's the way we feel.

Now let me describe what the final product will be. I am not sure whether the antacid report is in your folder—is it, Bob? No—O.K. I am sure you will shortly be able to have copies of the Antimicrobial I, so we can, at the moment, only refer to the Antacid because that's the only one that has been published. Once this is published in the Federal Register, you will be able to use that in terms of understanding the format. The regulations provide that you will divide up all active ingredients and claims—and you have to look at the labeling claims also—into three categories. Category One is the good guys. They are safe and effective and properly labeled. Category Two is the bad guys. They are the ones that are unsafe or ineffective or improperly labeled. Category Three are in the gray zone, they are conditions under which we do not have sufficient information to make a competitive decision, and for which you will recommend further testing of one kind or another.

Now, at this point, I would like to mention further testing for Category Three because that is probably, from our standpoint, one of the most important issues. It is always easier for any scientist to say, "We do not have enough information and there ought to be some further testing." It's always nice to have more data than you do to make any decision. (I was in a meeting last night where the National Academy of Sciences had a large number of very basic research. There was no issue on which they did not say, "We need more information." After a while I admonished them with the fact that in the three years I have been with the Food and Drug Administration, I cannot recall one decision we made on which we had enough information to make it. We're in the real world where you have to make decisions on the basis of not having every last piece of data that we would like to have.)

But there are, nevertheless, some instances where quite probably you will say that a type of study is needed and where I think any reasonable scientist would agree with you. The critical thing there is for you to say what study is needed. It isn't enough to say in general terms ingredient "X" has a paucity of information about it. It needs further testing, period. Then go on to the next issue. What type of testing? Does it need teratogenicity testing? Does it need reproduction studies? Does it need a two-year chronic II species feeding study? Or does it need none of those and instead it needs just one simple adequate and well-controlled clinical study of humans?

If you write a report that leaves that kind of issue open, then in a sense you'll be abdicating your primary responsibility of telling us not only what is safe and effective, and what isn't safe and effective, but the in-between category—what needs to be done to resolve the issue. Our end objective is to resolve all these issues one way or another—up, down, or further testing. That, as you know, Wally, has been one of my biggest disputes with the Antimicrobial I Panel, and in all candor, I still feel that the final report doesn't go far enough in being specific. It does in some areas, where it spells out what testing is needed. In other areas I still find it a bit fuzzy, and let me tell you we'll be back to you on those. That's a forewarning to Antimicrobial II as well as Antimicrobial I.

In all seriousness, I think it's terribly important. I think I can state from the work that has gone on so far that the position of industry has uniformly been this: if you will tell us what testing to do we'll do it. I can understand that frustration. They frequently get from FDA, from the public, from the academic community, "There isn't enough data." Then they say, "What do you want?" Then they are told, "Well, you figure that out, I'm not going to tell you what we want." I don't feel the government should be in that position. If we say that a drug needs further testing, either the Panel or the Food and Drug Administration is going to have to lay out. . . . 1, 2, 3, 4 . . . here's what you've got to do. Now, sometimes, after doing the 1, 2, 3, and 4 something else will arise and maybe we'll need further information, but we've got to be as definitive as we can.

PANEL MEMBER. There was a fear that if the Panel [i.e. Antimicrobial I] said to do 1, 2, 3, and 4 and something turned up in 1, 2, 3, and 4 that we didn't anticipate, a stamp of approval would have been put on it anyway.

Mr. HUTT. I think the way to get around that is to write in the report that this is the initial testing that will be done. If nothing turns up this would appear to be all that's required. If new questions arise in the course of that testing, obviously those must be pursued. You always leave an escape hatch of that type. I think it might be useful, in light of your experience with Antimicrobial I in this regard, Wally, if, as you go along, a lack of data crops up, you make notes in your minutes of the meetings going along and say, "This is the type of testing that should be done for this particular ingredient," or whatever. Then you will have an ongoing decision that can be reflected in the final report.

There is, obviously, need for full discussion on why the Panel arrives at its conclusions that it does reach. I guess that all I need to do there is hold this [i.e. Antimicrobial I Report] up and say that is exactly what has been done here. It is a superb exposition, not just decisions reached, but the rationale behind them, the scientific literature, the unpublished data, everything else that has gone into those decisions. It has been painful, many times, to get to that point because we do impose, and we feel obligated to impose, two standards: (1) high quality in terms of articulation on a scientific basis of the conclusion, (a single conclusionary sentence is never going to suffice); and, (2) that it be written in a form that not just the most esoteric scientist is going to understand, but that judges and lawyers can also understand as well as laymen. Now I emphasize judges and lawyers for one very good reason, and this is what always upset Charlie Edwards and now upsets Mac Schmidt. I continually have to point out that if there is ever any dispute about this, it is judges and lawyers who will decide it because that's the way the court system works. If the industry challenges it—which they are absolutely free to do and should do if they disagree with it—they will appeal it to the courts and the judge doesn't have a Ph.D. in pharmacology. He has an LLB in law. He doesn't know any more about it than I do, so it's got to be understandable and reasonable to him as well as to other laymen, in addition to being scientifically sound. We had lots of thought with that in Antimicrobial I in making sure that we would meet that standard. I think it meets that standard. I know it does. So, the end process is a report of this nature.

Now, as is true of the entire governmental process, ultimately it is the Commissioner of Food and Drugs who is required by law to make the decision. Your report is a report and recommendations to the Commissioner. It then goes through a procedure whereby, as with Antimicrobial I, it is reprinted, every word.

There is literally not one comma changed from what the Panel report said in the Federal Register. Time is given for comment. We analyze the comments with the help of the Panel, because we do go back and involve the Panel in coming out with a Tentative Final Order. Again, objections can be filed. A public hearing will be held by the Commissioner, presiding over it personnally. Then comes a Final Order, which is, of course where the Antacid document is right at the moment. From there the industry, as has been pointed out, can appeal that to the courts. Once it is appealed to the courts and upheld—if it is upheld—it is at that point the law and it must be obeyed. That describes a little bit of the process, and I think the importance of what you are doing.

That is all I have to say in terms of the OTC Review as an OTC Review. There are two other points that I always discuss briefly. That is conflicts of interest and the confidentiality of the scientific material that has been submitted to us and has been sent out to the Panel. I have one suggestion to cover both of these situations, which, I think if you follow will be very, very easy on you and maybe difficult on us, but I think that's where it should be. There is both a conflict-of-interest law which says that it is a criminal offense for any governmental employee (and whether you like it or not you are government employees) to have a conflict of interest or to release confidential information that has been submitted to the Federal Administration. Now, in light of those provisions, my rule is very simple. If someone calls anybody or writes anybody and asks you to participate, say, in working for a pharmaceutical company or if someone wants to see some of the material that's been sent out to you, or if you want to show a colleague one of the papers, all you have to do is call us. If we say "yes," then we're on the hook and you're off. It's very simple. If we can give you a definitive answer we have the legal authority to do it. If you make that decision on your own, then you're on the hook and we're off and that's not the way we think it ought to be. We've not had any problem at all, I might add, in this entire affair because in every Panel people have simply picked up the telephone and called

Bob Pinco and called me or whoever, and said, "I was just asked to review a protocol for the XYZ Pharmaceutical Company. Is it all right?" We said "yes" or "no." We usually looked into it pretty carefully and got enough information to make a good judgment. It's such a simple rule to follow and if you follow it you are absolutely protected. It's even more relevant today with what's going on up on The Hill in light of the current climate. This isn't something that one ought to treat lightly. You're better safe than sorry. We will respond to those kinds of inquiries on an absolutely immediate basis and will get back to you with a clear answer whenever you have any question. We are here to serve you and you're here serving the public.

Now, I would just close with one final comment and I know that it's been said, probably much better by you, Wally, and I think Carl's earlier remarks said the same thing. This kind of project is viewed by FDA—and when I say FDA, I mean everyone from the Commissioner on down—as absolutely the most important project that FDA has undertaken in the last three years. Stop to think about what we are doing. Since the beginning of time there has never been an attempt to really take a good hard look at the scientific basis for the safety, effectiveness, and labeling of OTC drugs—not only in this country but in any other country since the beginning of time. We've never, in the history of the FDA, done it, despite the 1906, the 1938, the 1962 legislation. This is the first time. We are trying, obviously, the impossible—i.e. in five years to cover two hundred thousand drugs. There's only one way to do it and that is with enormous hard work, both inside the Agency and in Panels like this. We realize we impose upon you. I can't think of how much we've imposed upon you, Wally, Frank, and members of Antimicrobial I Panel. We kept them a year after they thought they had finished their project because we wanted to make sure that it was the best damn report that had ever been issued—and it is. There's nothing in the field that compares with it.

Now, that's the kind of work that I feel demands a great deal of you and us. I really do challenge you to find anything that you've worked on that has greater significance and has greater impact on the public and on the future of this country in terms of good, sound medical drugs on the market that help the people of the country. To me it's just enormously important and I think you're going to find as you get into it you'll feel quite the same way.

MAY 24, 1975.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: In the course of the recent hearings on the OTC drug review, reference was made to a letter from Dr. Ingelfinger to Dr. Simmons dated December 11, 1972, in which Dr. Ingelfinger expressed concern about my insistence on detailed documentation of, and justification for, the Panel's conclusions. I testified about my recollection of the circumstances surrounding that letter.

In order to verify my recollection, I subsequently telephoned Dr. Ingelfinger about it. A copy of my telephone memorandum, which has been approved by Dr. Ingelfinger, is enclosed. In order to make the record complete on this matter, I am requesting that this letter and the enclosed telephone memorandum be included in the printed record of the hearing at the point where this matter was discussed.

Sincerely yours,

PETER BARTON HUTT.

MEMORANDUM OF TELEPHONE CONVERSATION

On May 14, 1975, I telephoned Dr. Franz Ingelfinger to relate to him the fact that his letter to Dr. Simmons dated December 11, 1972, had been the subject of discussion at the hearing held by Congressman Fountain on May 12, 1975. I read to him the pertinent portion of his letter and the resulting Washington Post article.

I said to Dr. Ingelfinger that my recollection was that he and I had subsequently discussed his letter when he was in Washington for the press conference on the antacid report, and at that time he had said that he fully understood the reasons for my insisting upon the best possible report and that he believed that the report had in fact been improved as a result of our work together.

Dr. Ingelfinger said that, although he did not recall the details of his letter or our subsequent conversation, what I had said at the hearing did represent his

general recollection of the matter. He understood that I was performing a necessary legal function. He said that, if anyone had asked him about our relationship, he would have described it as very helpful and cordial.

Dr. Ingelfinger said that he did not believe that his letter was at all directed to the Alka-Seltzer issue. Rather, it was simply the result of general irritation about the need for additional work, when the Panel thought that its work had been completed, and in particular my insistence that the Panel try to be very specific and to document every statement. The Panel was also concerned at what it perceived as my efforts to express in "hard" legally satisfactory language opinions based on relatively "soft" clinical data.

Dr. Ingelfinger expressed surprise that the transcript of the closed portions of the Panel meetings had in any way been made public. It was his understanding that this would not be done.

I asked Dr. Ingelfinger whether he had ever met with Dr. Edwards to discuss the Alka-Seltzer issue. He stated that he had met with Dr. Edwards, and that Dr. Simmons and I had been present during part of the meeting, at the time that we had asked him whether the report prepared by Dr. Nestor of FDA should be sent to the entire Panel. This would have been before the December 1972 meeting, probably in late October or early November 1972. The meeting was held at the downtown FDA building (FOB–8). He did not subsequently talk to Dr. Edwards about the report.

Dr. Ingelfinger said he was sorry that the letter had caused me embarrassment. I replied that this was simply part of my job and must be expected by any government official.

I promised to send Dr. Ingelfinger a copy of his letter, the article by Morton Mintz, and the pertinent parts of the hearing transcript. He could then get in touch with Congressman Fountain if he wished to add to or correct the record in any way.

PETER BARTON HUTT.

Attached is a memorandum of meeting between Mr. Gilbert S. Goldhammer of the Subcommittee staff and Mr. Armond M. Welch, Acting Executive Secretary, OTC Antacid Review Panel, Division of OTC Drug Evaluation, FDA, to discuss the labeling change for antacids which was circulated to the OTC Panel on June 3, 1973. At the time of the meeting, Mr. Goldhammer agreed to the inclusion in the record of this hearing a copy of this memorandum and attachments.

MEMORANDUM OF VISIT JUNE 5, 1973

Mr. Gilbert S. Goldhammer, Consultant Subcommittee on Intergovernmental Relations and Human Resources, Committee of Government Operations, House of Representatives and Armond M. Welch—Acting Executive Secretary, OTC Antacid Review Panel, Division of OTC Drug Evaluation, FDA, Bureau of Drugs.

Mr. Goldhammer visited me as per arrangements through Mr. Wetherell of Office of Legislative Services (OLS). At Mr. Goldhammer's request I outlined, as I recalled, the circumstances leading up to revision on 1–3–73 of page 46 of the Antacid Panel's draft report as follows:

In my review of the Antacid draft is appeared to me that the indications for use was negative in concept whereas I understood that the Panel had intended the indications for use to be written in a positive tone. In other words, the consumer was to be told in clear concise language what combination of symptoms the product was intended to alleviate.

In Mr. Yingling's absence I contacted Dr. Novitch and informed him of my plans to discuss the matter with Dr. Ingelfinger and if he concurred, with the Panel members. I then telephoned Dr. Ingelfinger and he readily agreed. To the best of my recollection, each Panel member was telephoned and each concurred. Subsequently, on January 3, 1973, I sent each member the proposed revision (copy enclosed). On January 5, 1973 I circulated a memorandum (copy enclosed) regarding the scheduled telephone conference.

Mr. Goldhammer displayed a copy of the Miles Labs/Commissioner document and inquired about my seeing the document before our contacting the Panel and why it was not filed with the Hearing Clerk's Office.

I advised him that while I do recall seeing this document, it was not before my telephone calls.

The document had not been filed because it was not one that had been reviewed by the Panel.

We discussed the OTC document logging system and I showed him the receiving log. He inquired about a Plough submission dated January 3, 1973 which was sent to the Panel and we went to the Hearing Clerk's Office where the document was located and at this request, a copy was made for him (a duplicate is attached).

ARMOND M. WELCH.

ANTACID PANEL MEMBERS AND CONSULTANTS, JANUARY 3, 1973

Panel Administrator.
Page 43 Revision.

I have redrafted Paragraph 1 of this page. The proposed revision has been discussed with Dr. Ingelfinger, and will be discussed further in the conference call scheduled for Tuesday, January 9 at 1:00 P.M., Eastern Daylight Saving Time.

ARMOND M. WELCH.

Enclosure.

REVISED JANUARY 3, 1973

D. *Drugs combining antacid and other active ingredients*

The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor a corrective for an antacid side effect, will contribute to the product's safety and effectiveness for use in antacid therapy alone. The addition of non-antacid or non-corrective ingredients may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor a corrective for an antacid side effect should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and non-antacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief provided by both types of active ingredients. The indication section of the labeling should state clearly that the combination should be used only when heartburn and/or acid indigestion and/or sour stomach are accompanied by indications for an analgesic. Such a product is not appropriate for peptic ulcer and related * * *.

JANUARY 5, 1973.

Executive Secretary, Antacid Panel.
Telephone Conference Re Antacid Report.

Conference telephone arrangements have been made for the Antacid Panel members to discuss, and hopefully to adopt, the December 22 draft report.

Since Dr. Spiro will not be able to participate, Dr. Ingelfinger plans to contact him and determine for the panel the reports acceptability. (Dr. Spiro has indicated to me that the report is acceptable.)

Consumer and Industry Liaison members, as well as appropriate FDA personnel, will listen-in via the speaker phone in the Commissioner's Conference Room.

As requested by Dr. Ingelfinger arrangements have been made for a stenotypist.

I have suggested a revision of page 43 (dated 1-3-73) which has been distributed. Dr. Ingelfinger has suggested other changes by telephone and as those changes are made I will forward them to you.

ARMOND M. WELCH.

Attached is a certified copy of page 46 of the Panel Report as well as a copy of the Federal Register of April 5, 1973. As these documents demonstrate, the third citation ("3) Jennings, GH; 'Alka Seltzer and Haematemesis', Letter to the Editor; Brit. Med. J., 16:475, 1963") was deleted from the Federal Register document and in lieu thereof the citation for "(4) Jennings, G. H.; 'Causal influences in

Haematemesis and Melaena,' Gut, 6:1–13, 1965" was inserted. The Federal Register document carries four references in addition to the ones cited in the Panel Report.

EXHIBIT C

(Page 46)

* * * *antacid-aspirin combinations are irrational for antacid use alone and therefore should not be labeled or marketed for such use. Not only are OTC antacids sometimes indiscriminately used, which may lead to aspirin toxicity with such combinations, but aspirin also has a potential for damaging the gastrointestinal mucosa by the topical action of breaking the mucosal barrier or by other mechanisms.*[1]

CITATIONS

1. Brodie, DA and Chase, BJ; "Role of Gastric Acid In Aspirin-Induced Gastric Irritation In The Rat", Gastroenterology, *53*: 604–610, 1967.

2. Grossman, MI; Matsumoto, KK; Lichter, RJ; "Fecal Blood Loss Produced By Oral and Intravenous Administration of Various Salicylates", Gastroenterology, *40*: 383–388, 1961.

3. *Jennings, GH; "Alka Seltzer and Haematemesis", Letter to the Editor; Brit. Med. J., 16: 475, 1963.*

NOTE.—Delete *Jennings* citation. See memorandum comment.[2 3]

2. The Panel concludes that it is not safe and effective concurrent therapy to add an anticholinergic ingredient to an OTC antacid product, because optimal use of antacids and * * *.

Certified to be a true copy of the original.

HENRY DAUSCH.

[From the Federal Register, Apr. 5, 1973]

PROPOSED RULES

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor a corrective for an antacid side effect should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and nonantacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product has concurrent symptoms which require the relief provided by both types of active ingredients. The indication section of the labeling should state clearly that the combination should be used for heartburn and/or acid indigestion and/or sour stomach only when these symptoms are accompanied by indications for an analgesic. Such a product is not appropriate for peptic ulcer and related disorders. Any analgesic ingredient that is generally recognized as safe and effective (see analgesic Monograph) may be used as the analgesic ingredient.

2. The Panel concludes that it is rational to include a nonantacid laxative ingredient in an antacid if the laxative is solely for the purpose of counteracting the constipating action of one or more of the antacid ingredients. Any laxative action ingredient that is generally recognized as safe and effective (see laxative Monograph) may be used as the laxative ingredient. No labeling claim for the laxative effect would be truthful, because the amount of nonantacid laxative ingredient present should not cause laxation, but only counteract the constipating effect of the antacid.

Comment. Any other combination of antacid with nonantacid active ingredients should be permitted by the Food and Drug Administration only after it is shown that the conditions for a combination drug set out in the regulations have been met. The Panel is unaware of any other such combinations which meet these conditions at the present time.

II. *Conditions under which antacid products are not generally recognized as safe and effective or are misbranded.* The use of antacids under the following

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[1] Blue ink underlined portions appear in italic.

[2] In the original submission, Miles Laboratories' "Notes" appear in the left hand margins next to the pertinent portions of the draft report.

[3] At this "Note" there is a handwritten arrow with the word "out" pointed to the Jennings citation (3).

conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Panel concludes that the ingredients, labeling, and combination drugs involved should be removed from the market until scientific testing supports their use.

A. *Active ingredients.* No active ingredients for which data were submitted to the Panel and that is not included in Category I or Category III has, in the Panel's opinion, been shown by adequate and reliable scientific evidence to be safe and effective.

B. *Labeling.* The Panel concludes that it is not truthful and accurate to make claims or to use indications on the package label that the product may directly affect "nervous or emotionl disturbances," "excessive smoking," "food intolerance," consumption of "alcoholic beverages," "acidosis," "nervous tension headaches," "cold symptoms," and "morning sickness of pregnancy" since the relationship of such phenomena to gastric acidity is both unproven and unlikely.

C. *Drugs combining antacid and other active ingredients.* 1. Although the Panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for treatment of concurrent symptoms, it concludes that fixed antacid-aspirin combinations are irrational for antacid use alone and therefore should not be labeled or marketed for such use. Not only are OTC antacids sometimes indiscriminately used, which may lead to aspirin toxicity with such combinations, but aspirin also has a potential for damaging the gastrointestinal mucosa by the topical action of breaking the mucosal barrier or by other mechanisms.

In experiments in man and animals unbuffered aspirin causes greater visible gastric mucosal damage and more gastrointestinal blood loss than strongly buffered aspirin in solution, which causes little or none of these experimental forms of damage. However, the actual clinical condition or major gastrointestinal hemorrhage associated with aspirin ingestion has been seen with both unbuffered and strongly buffered aspirin in solution. There is inadequate evidence to establish whether the risk of clinically major gastrointestinal hemorrhage is less with strongly buffered aspirin in solution than with unbuffered aspirin. Because of this uncertainty and the lack of evidence of effectiveness of salicylate for antacid indications, benefit-risk considerations dictate that such a product not be indicated solely for antacid purposes.

CITATIONS

(1) Brodie, D. A. and Chase, B. J.; "Role of Gastric Acid in Aspirin-Induced Gastric Irritation in the Rat," Gastroenterology, *53*:604–610, 1967.

(2) Brown, R. K. and Mitchell, N.; "The Influence of Some of the Salicyl Compounds (and alcoholic beverages) on the Natural History of Peptic Ulcer," Gastroenterology, *31*:198–203, 1956.

(3) Grossman, M. I.; Matsumoto, K. K.; Lichter, R. J.; "Fecal Blood Loss Produced by Oral and Intravenous Administration of Various Salicylates," Gastroenterology, *40*:383–388, 1961.

(4) Jennings, G. H.; "Causal Influences in Haematemesis and Melaena," Gut, *6*:1–13, 1965.

(5) Langman, M. J. S.; "Epidemiological Evidence for the Association of Aspirin and Acute GI Bleeding," Gut, *11*:627–634, 1970.

(6) Leonards, J. R. and Levy, G.; "Reduction or Prevention of Aspirin-Induced Occult Gastrointestinal Blood Loss in Man," Clinical Pharmacology and Therapeutics, *10*:571–575, 1969.

(7) Thorsen, W. B. Jr.; Western, D.; Tanaka, Y. and Morrissey, J. F.; "Aspirin Injury to the Gastric Mucosa, Gastrocamera Observations of the Effect of pH," Archives of Internal Medicine, *121*:499–506, 1968.

2. The Panel concludes that it is not safe and effective concurrent therapy to add an anticholinergic ingredient to an OTC antacid product, because optimal use of antacids and anticholinergic drugs requires independent adjustment of dosages of each drug, because the addition of an anticholinergic drug in a concentration large enough to have detectable pharmacologic effects would result in a compound too toxic for use in self-medication, and because entirely safe amounts of anticholinergics have not been shown to affect gastric secretion or upper gastrointestinal symptoms. Since elderly persons number prominently among antacid users, cycloplegia and urinary retention induced by anticholinergic drugs is a definite risk. Thus, a fixed combination of antacid and anticholinergic will result, regardless of how formulated, in a mixture that is either unsafe or ineffective.

The same conclusions apply to combinations of antacids with sedative-hypnotic ingredients.

3. The Panel concludes that it is not rational concurrent therapy, for a significant portion of the target population for the label to claim that a combination product (e.g., mineral oil and magnesium hydroxide) is to be used both as an antacid and as a laxative if the laxative claim is supported by a nonantacid laxative ingredient.

The Panel recognizes that there are active antacid ingredients that may be effective as laxatives at higher doses than those used for antacid action. The Panel understands that the question whether such uses are appropriate will be reviewed by the Laxative Panel and, for this reason, takes no position on use these ingredients as laxatives.

4. The Panel is not aware of any study showing that the addition of an antipeptic agent to an antacid product increases the product's efficacy as an antacid or is otherwise effective as a means of managing upper gastrointestinal symptoms. All antacids are antipeptic in the sense that peptic activity is reduced as pH increases and pepsin is irreversibly inactivated at pH's above 7. No claim for antipeptic activity can be considered truthful and accurate until it is substantiated both by scientifically valid in vitro tests showing that the antipeptic action is substantially greater than that of an agent with only antacid action (such as sodium bicarbonate), and it is proved by studies that the antipeptic activity is clinically meaningful and therefore contributes to the product's effectiveness.

5. The Panel concludes that the addition of proteolytic agents or bile or bile salts to antacid products is unsafe. Since pepsin is presumably involved in the pathogenesis of peptic ulcer, the addition of pepsin to antacid products may be potentially harmful. Since bile and bile salts can damage gastric mucosa, and since they may be involved in the pathogenesis of gastric ulcer, these substances should not be permitted in antacid products.

6. The Panel concludes that the addition of an antiemetic to an antacid product is not rational therapy for a significant portion of the target population.

Attached are copies of the paragraph under discussion from the Panel Report, the proposed regulation, the tentative final order, and the final order. The only change was in the final regulation which added the phrase, "is marketed in a form intended for ingestion as a solution." The explanation for this change is provided in the insert for the record on page 168, line 9.

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(2) An antacid may contain any generally recognized safe and effective analgesic ingredient(s) (see analgesic Monograph) if it is indicated for use solely for the concurrent symptoms involved (e.g., headache and acid indigestion).

(h) *Inactive ingredients.*—The amount of lactose in a maximum daily dosage may not exceed 5 gm. per day.

FRANZ J. INGELFINGER, M.D.,
Antacid Panel Chairman, January 23, 1973.

Certified to be a true copy of the original.

ROBERT C. WETHERELL, Jr.

[From the Federal Register, Apr. 5, 1973]

PROPOSED RULES

(*c*) Place empty beaker on stirrer, add stirring bar, determine setting for stirring at 240 r.p.m. throughout.

(*d*) Add one unit dose of antacid and 50 ml. 0.1 N HCl to beaker. Acid or antacid may be added first. If antacid is in tablet form, it may be added as whole tablets or as particles except that if label states that tablets are to be swalloewd whole, whole tablets should be used in the test. Particles should be prepared from ground tablets taking particles that pass a 12 standard mesh sieve and are held by a 16 standard mesh sieve. If particles are used, the weight of particles should equal the weight of a unit dose.

(*e*) Stir for exactly 10 minutes at 240 r.p.m.
(*f*) Read and record pH.
(*g*) If pH is 3.5 or greater, proceed; if pH is below 3.5, stop test.
(*h*) If pH in paragraph (*g*) of this section is 3.5 or greater, add 1.0 N HCl from buret to bring pH to 3.5. Continue to add 1.0 N HCl at the rate required to hold pH at 3.5.
(*i*) Exactly 5 minutes after beginning addition of 1.0 N HCl (15 minutes after adding antacid) read and record ml. of 1.0 N HCl used.
(*j*) Calculation: 5 mEq. (in 50 ml. 0.1 N HCl used in 1st 10 min.) +number of ml. 1.0 N HCl added during period 10 to 15 min.=mEq. acid neutralized in 15 min.
(iii) The formulation and/or mode of administration of certain products (e.g., in chewing gum form) may require modification of this in vitro test.
(2) *Aluminum-containing active ingredients.*
(i) Aluminum carbonate.
(ii) Aluminum hydroxide (as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).
(iii) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid.
(iv) Aluminum phosphate, maximum daily dosage limit 12.5 grams.
(v) Dihydroxyaluminum sodium carbonate.
(3) *Bicarbonate-containing active ingredients.* Bicarbonate ion, maximum daily dosage limit 200 mEq. for persons up to 60 years old and 100 mEq. for persons 60 years or older.
(4) *Bismuth-containing active ingredients.*
(i) Bismuth aluminate.
(ii) Bismuth carbonate.
(iii) Bismuth subcarbonate.
(iv) Bismuth subgallate.
(v) Bismuth subnitrate.
(5) *Calcium-containing active ingredients.* Calcium, as carbonate or phosphate, maximum daily dosage limit 160 mEq. calcium (e.g., 8 grams calcium carbonate).
(6) *Citrate-containing active ingredients.* Citrate ion, as citric acid or salt, maximum daily dosage limit 8 grams.
(7) *Glycine (aminoacetic acid).*
(8) *Magnesium-containing active ingredients.*
(i) Hydrate magnesium aluminate activated sulfate.
(ii) Magaldrate.
(iii) Magnesium aluminosilicates.
(iv) Magnesium carbonate.
(v) Magnesium glycinate.
(vi) Magnesium hydroxide.
(vii) Magnesium oxide.
(viii) Magnesium trisilicate.
(9) *Milk solids, dried.*
(10) *Phosphate-containing active ingredients.*
(i) Aluminum phosphate, maximum daily dosage limit 8 grams.
(ii) Mono or dibasic calcium salt, maximum daily dosage limit 2 grams.
(iii) Tricalcium phosphate, maximum daily dosage limit 24 grams.
(11) *Potassium-containing active ingredients.*
(i) Sodium bicarbonate or carbonate, maximum daily dosage limit 200 meq of sodium for persons up to 60 years old and 100 meq of sodium for persons 60 years or older, and 200 meq of bicarbonate ion for persons up to 60 years old and 100 meq of bicarbonate ion for persons 60 years or older.
(13) *Silicates.*
(i) Magnesium aluminosilicates.
(ii) Magnesium trisilicate.
(14) *Tartrate-containing active ingredients.* Tartaric acid or its salts, maximum daily dosage limit 200 mEq. (15 grams) of tartrate.
(b) *Indications.* The labeling of the product represents or suggests the product as an "antacid," to alleviate the symptoms of "heartburn," "sour stomach," or "acid indigestion."

(c) *Warnings.* The labeling of the product contains the following warnings:

(1) "Do not take more than ____ (maximum recommended daily dosage, broken down by age groups if appropriate, expressed in units such as tablets or teaspoonfuls) in a 24-hour period except under the advice and supervision of a physician."

(2) "Do not use the maximum dosage of this antacid for more than 2 weeks except under the advice and supervision of a physician."

(3) For products which cause constipation in 5 percent or more of persons who take the maximum recommended dosage: "May cause constipation."

(4) For products which cause laxation in 5 percent or more of persons who take the maximum recommended dosage: "May have laxative effect."

(5) For products containing more than 50 mEq. of magnesium in the recommended daily dosage: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(6) For products containing more than 5 mEq. sodium in the maximum recommended daily dose: "Do not use this product except under the advise and supervision of a physician if you are on a sodium restricted diet."

(7) For products containing more than 25 mEq. potassium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(d) *Directions for use.* The labeling of the product contains the recommended dosage per time interval, broken down by age groups if appropriate, followed by "except under the advice and supervision of a physician."

(e) *Statement of active ingredients.*

(1) The labeling of the product contains the quantitative amount of each active ingredient expressed in terms of the dosage unit stated in the directions for use (e.g., tablet, teaspoonful).

(2) The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq. (5 mg.) or higher.

(f) *Ethical labeling.* The labeling of the product provided to physicians (but not to the general public):

(1) Shall contain the neutralizing capacity of the product, as calculated in paragraph (a)(1)(ii)(*j*), expressed in terms of the dosage recommended per minimum time interval or, if the labeling recommends more than one dosage, in terms of the minimum dosage recommended per minimum time interval.

(2) Shall, if the product is an aluminum or kaolin-containing antacid, contain a warning that absorption of other drugs may be interfered with by the aluminum or kaolin in the product.

(3) May contain as additional indications peptic ulcer, gastritis, and peptic esophagitis.

(g) *Combination with nonantacid active ingredients.*

(1) An antacid may contain any generally recognized safe and effective nonantacid laxative ingredient (see laxative Monograph) to correct for constipation caused by the antacid. No labeling mention of the laxative ingredient or claim of laxative effect may be used for such a product.

(2) An antacid may contain any generally recognized safe and effective analgesic ingredient(s) (see analgesic monograph) if it is indicated for use solely for the concurrent symptoms involved (e.g., headache and acid indigestion).

(h) *Inactive ingredients.* The amount of lactose in a maximum daily dosage may not exceed 5 gm. per day.

Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before June 4, 1973. Such comments should be addressed to the hearing clerk, Department of Health, Education, and Welfare, room 6-88, 5600 Fishers Lane, Rockville, Md. 20852, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before July 2, 1973. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: March 9, 1973.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc. 73-5657 Filed 4-4-73; 8:45 am]

[From the Federal Register, Nov. 12, 1973]

(d) *Directions for use.* The labeling of the product contains the recommended dosage per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age groups if appropriate, followed by "except under the advice and supervision of a physician."

(e) *Statement of sodium containing ingredients.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq. (5 mg) or higher.

(f) *Ethical labeling.* The labeling of the product provided to physicians (but not to the general public):

(1) Shall contain the neutralizing capacity of the product, as calculated in paragraph (a) (1) (ii) (*j*) of the section, expressed in terms of the dosage recommended per minimum time interval or, if the labeling recommends more than one dosage, in terms of the minimum dosage recommended per minimum time interval. The neutralizing capacity value reported in such labeling may not exceed ten percent of the determined lower limit. Such labeling may indicate the value at the time of manufacture and/or after a specified period of time. No product may be marketed with an acid neutralizing capacity below 5 mEq.

(2) Shall, if the product is an aluminum or kaolin-containing antacid, contain a warning that absorption of other drugs may be interfered with by the aluminum or kaolin in the product.

(3) May contain an indication for the symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, and hiatal hernia.

(g) *Combination with nonantacid active ingredients.* (1) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient (see laxative monograph) to correct for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(2) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s) (see analgesic monograph) if it is indicated for use solely for the concurrent symptoms involved (e.g., headache and acid indigestion).

(3) An antacid may contain any generally recognized as safe and effective antiflatulent ingredient (see antiflatulent monograph) if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

§ 130.306 Antiflatulent.

An over-the-counter antiflatulent product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 130.302.

(a) *Active ingredient(s).* Simethicone. Maximum daily dose 500 mg.

(b) *Indications.* The labeling of the product represents or suggests the product as an "antiflatulent" to alleviate the symptoms of gas.

(c) *Directions for use.* The labeling of the product contains the recommended dosage per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age group if appropriate, followed by "except under the advice and supervision of a physician."

(d) *Ethical labeling.* The labeling of the product provided to physicians (but not to the general public) may contain as additional indications postoperative gas pain.

(e) *Combination with non-antiflatulent active ingredient(s).* An antiflatulent may contain any generally recognized safe and effective antacid ingredient(s) (see antacid monograph) if it is indicated for use solely for the concurrent symptom of gas associated with heartburn, sour stomach or acid indigestion.

Interested persons may file written objections and request an oral hearing before the Commissioner regarding this proposal on or before December 12, 1973. Request for an oral hearing must specify points to be covered and time requested.

All objections and requests shall be addressed to the Hearing Clerk, Food and Drug Administration, Room 6–86, 5600 Fishers Lane, Rockville, MD 20852, and

may be accompanied by a memorandum or brief in support thereof. Received objections and requests may be seen in the above office during working hours, Monday through Friday. Any scheduled oral hearing will be announced in the FEDERAL REGISTER.

Dated: November 2, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc. 73-23927 Filed 11-9-73; 8:46 am]

[21 CFR Part 130]

OVER-THE-COUNTER DRUGS

PROPOSED PROCEDURES REGARDING PUBLIC COMMENT ON REVIEW PANEL REPORTS

Section 130.301(a)(6) of the procedures governing the over-the-counter (OTC) drug review provides that, after an advisory review panel issues its report to the Commissioner of Food and Drugs, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing his proposed action.

In reviewing the report of the first OTC advisory review panel, on antacids, it became apparent to the Commissioner that it would be more expeditious to publish the panel's report and proposed monograph, without change, in order to obtain full public comment before he made any decision on the matters involved. It appears likely that this procedure may also be useful for handling the reports of other OTC advisory review panels. The Commissioner believes that this procedure is within the intent of the existing regulation, but comments on the proposed antacid monograph contended that it is not. Accordingly, to clarify this matter the Commissioner is proposing to revise § 130.301(a)(6) explicitly to incorporate this procedure.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243, as amended; (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes to amend 21 CFR 130.301(a)(6) by adding the following sentence to the end of the undesignated paragraph following subdivision (iv), to read as follows:

§ 130.301 Over-the-counter (OTC) drugs for human use; procedures for rulemaking for the classification of OTC drugs as generally recognized as safe and effective and not misbranded under prescribed, recommended, or suggested conditions of use.

* * * * * * *

(a) * * *
(6) * * *
(iv) * * *

* * * The Commissioner may satisfy this requirement by publishing in the Federal Register a proposed order summarizing the full report of the advisory review panel, containing its conclusions and recommendations, in order to obtain full public comment before undertaking his own evaluation and decision on the matters involved.

* * * * * * *

Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before December 12, 1973. Comments should be filed with the Hearing Clerk, Food and Drug Administration, Room 6-86, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated November 2, 1973.

A. M. SCHMIDT,
Commissioner of Foods and Drugs.

[FR Doc.73-23926 Filed 11-9-73;8:46 am]

[From the Federal Register, June 4, 1974]

* * * daily dosage limit 200 mEq. for persons up to 60 years old and 100 mEq. for persons 60 years or older.

(e) Bismuth-containing active ingredients:
(1) Bismuth aluminate.
(2) Bismuth carbonate.
(3) Bismuth subcarbonate.
(4) Bismuth subgallate.
(5) Bismuth subnitrate.

(d) Calcium-containing active ingredients: Calcium, as carbonate or phosphate; maximum daily dosage limit 160 mEq. calcium (e.g., 8 grams calcium carbonate).

(e) Citrate-containing active ingredients: Citrate ion, as citric acid or salt; maximum daily dosage limit 8 grams.

(f) Glycine (aminoacetic acid).

(g) Magnesium-containing active ingredients:
(1) Hydrate magnesium aluminate activated sulfate.
(2) Magaldrate.
(3) Magnesium aluminosilicates.
(4) Magnesium carbonate.
(5) Magnesium glycinate.
(6) Magnesium hydroxide.
(7) Magnesium oxide.
(8) Magnesium trisilicate.

(h) Milk solids, dried.

(i) Phosphate-containing active ingredients:
(1) Aluminum phosphate; maximum daily dosage limit 8 grams.
(2) Mono or dibasic calcium salt; maximum daily dosage limit 2 grams.
(3) Tricalcium phosphate; maximum daily dosage limit 24 grams.

(j) Potassium-containing active ingredients:

(1) Potassium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older.

(2) Sodium potassium tartrate.

(k) Sodium-containing active ingredients:

(1) Sodium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of sodium for persons up to 60 years old and 100 mEq. of sodium for persons 60 years or older, and 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older. The warning required by § 330.1(g) concerning overdoses is not required on a product containing only sodium bicarbonate powder.

(2) Sodium potassium tartrate.

(l) Silicates:

(1) Magnesium aluminosilicates.

(2) Magnesium trisilicate.

(m) Tartrate-containing active ingredients. Tartaric acid or its salts; maximum daily dosage limit 200 mEq. (15 grams) of tartrate.

§ 331.15 Combination with nonantacid active ingredients.

(a) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient to correct for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

(c) An antacid may contain any generally recognized as safe and effective antiflatulent ingredient if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

Subpart C—Testing Procedures

§ 331.20 Apparatus and reagents.

(a) pH meter, equipped with glass and saturated calomel electrodes.
(b) Magnetic stirrer.
(c) Magnetic stirring bars (about 40 mm. long and 10 mm. in diameter).
(d) 50 ml. buret.
(e) Buret stand.
(f) 100 ml. beakers.
(g) 250 ml. beakers.
(h) 10 mi., 20 ml. and 30 ml. pipets calibrated to deliver.
(i) Tablet comminuting device.
(j) A number 20 and 100 U.S. standard mesh sieve.
(k) Tablet disintegration apparatus.
(l) 0.1 N, 0.5 N and 1.0 N hydrochloric acid.
(m) 0.5 N sodium hydroxide.
(n) Standard pH 4.0 buffer solution (0.05 M potassium hydrogen phthalate).
(o) 95 percent ethanol.
(p) Distilled Water.

§ 331.21 Determination of percent contribution of active ingredients.

To determine the percent contribution of an antacid active ingredient, place an accurately weighed amount of the antacid active ingredient equal to the amount present in a unit dose of the product into a 250 ml. beaker. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix thoroughly to wet the sample (ethanol may affect the acid neutralizing capacity). Add water to a volume of 70 ml. and mix on magnetic stirrer at 300 ± 30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.26 and calculate the percent contribution of the antacid active ingredient in the total product as follows:

$$\text{Percent contribution} = \frac{\text{Total mEq. Antacid Active Ingredient} \times 100}{\text{Total mEq. Antacid Product}}$$

§ 331.22 Reagent standardization.

Standardize the sodium hydroxide (NaOH) and Hydrochloric acid (HCl) solutions according to the procedures in the United States Pharmacopeia XVIII (NaOH page 1036 and HCl page 1034) or the Official Methods of Analysis of the Association of Official Analytical Chemists, 11th Ed., 1970, (NaOH page 876 and HCl page 873).[1]

§ 331.23 Temperature standardization.

All tests shall be conducted at 25° C ± 3°.

§ 331.24 Tablet disintegration test.

A table disintegration test shall be performed on tablets that are not to be chewed following the procedures described in the United States Pharmacopeia XVIII (page 932). If the label states the tablet may be swallowed, it must disintegrate within a 10-minute time limit pursuant to the test procedure using simulated gastric fluid test solution without enzymes, the United Syates Pharmacopeia XVIII page 1026, rather than water as the immersion fluid.

§ 331.25 Preliminary antacid test.

(a) *pH meter.* Standardize the pH meter at pH 4.0 with the standardizing buffer and check for proper operation at pH 1 with 0.1 N HCl.

(b) *Dosage form testing*—(1) *Liquid sample.* Place an accurately weighed (calculate density) and well mixed amount of the antacid product equivalent to the minimum labeled dosage; e.g., 5 ml., into a 100 ml. beaker. Add sufficient water to obtain a total volume of about 40 ml. and mix on magnetic stirrer at 300 ± 30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.25.

(2) *Chewable and non-chewable tablet sample.* Place an accurately weighed amount of a tablet composite equivalent to the minimum labeled dosage into a 100 ml. beaker. (The composite shall be prepared by determining the average weight of not less than 20 tablets and then comminuting the tablets sufficiently to pass through a number 20 U.S. standard mesh sieve and held by a number 100 U.S. standard mesh sieve.) Mix the sieved material to obtain a uniform

[1] Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, DC 20044.

sample. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix to wet the sample thoroughly (ethanol may effect the acid neutralizing capacity). Add water to a volume of 40 ml. and mix on magnetic stirrer at 300 ± 30 r.p.m. for about one minute. (Capsules should be tested in the same manner using the sieved capsule powder as the sample.) Analyze the sample according to the procedure set forth in § 331.25.

(3) *Effervescent sample.* Place an amount equivalent to the minimum labeled dosage into a 100 ml. beaker. Add 10 ml. water and swirl the beaker gently while allowing the reaction to subside. Add another 10 ml. of water and swirl the beaker gently. Wash down the walls of the beaker with 20 ml. of water and * * *.

The language in question appeared in 39 F.R. 19875 at Section 331.15 Combination with Nonantacid Active Ingredients. In that section in paragraph (b) the following statement appears:

> An antacid may contain any generally recognized as safe and effective analgesic(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion and is marketed in a form intended for ingestion as a solution.

The language that had appeared under Section 130.305(g)(2) (recodified as 331.15) in 38 F.R. 31269 (November 12, 1973) in the tentative final monograph and in 38 F.R. 8724 (April 5, 1973) in the proposed monograph were identical except for the last ten words "as is marketed in a form intended for ingestion as a solution."

At the hearing questions were asked whether or not FDA had made the change pursuant to a request by Miles Laboratory. Miles had submitted to the OTC Staff a memorandum dated December 29, 1972 which contained a copy of the Antacid Panel's Draft Report and the changes that Miles wished the Panel or FDA to make. The Panel report on pages 45 and 46 discussed the validity of combining an antacid with aspirin. Miles commented that the Panel had not distinguished the dry formula preparations from solutions in their review. I have included in this letter a copy of page 45 (Exhibit B) and 46 (Exhibit C) of the Report and the Miles insert (Exhibit A) stating the data did not support the panel's conclusion.

There is no request for a change in the marked up draft prepared by Miles concerning the use of an antacid analgesic only in solution.

A member of the General Counsel's staff has gone back and reviewed the comments on the Proposal and Tentative Final Orders in an attempt to determine whether or not a request as to a solution was made by any party. There is no written request in the public record for the words FDA added to the final monograph. However, a review of the data shows that Miles Laboratory had from the very beginning indicated that the product on which they submitted data was in solution. On June 4, 1973 Miles' comments in the Hearing Clerk's record on page 3 in paragraph A discuss an antacid analgesic in solution. In a December 12, 1973 letter commenting on the proposal Miles points out that the data submitted was on a highly buffered solution. There is also a statement in the transcript of the oral hearing held by Commissioner Schmidt at page 135 that the issues concern a buffered solution when aspirin is in a soluble and alkaline buffered form as an acetylsalicylate.

None of the comments submitted by Miles or any other party request the statement that the combination in the monograph only refers to a highly buffered solution. However, in review of the tentative final monograph it was realized by someone within the Agency that the only data submitted related to ingredients in solution for such a combination. If the solution language had not been added to the monograph, it would have been possible for a manufacturer to place a highly buffered analgesic antacid tablet in the marketplace for sale as generally recognized as safe and effective. The panel and the Agency clearly had no data to support that determination.

There is also no question that the change adding solution would have been made no matter what the source of the request had been. However, there is no showing in the record that Miles asked for those additional words in the monograph.

The review procedure of a proposed, tentative, and final monograph is designed to make sure that the final publication of a monograph is correct. Clearly, here the error became apparent before publication of the final monograph. That is how the system was designed to operate and it was effective.

EXHIBIT A

NOTE.—The underlined (italicized) portion of Section II.C.1 exhibits confusion between the reaction mixture of Alka-Seltzer and the dry ingredients from which the tablet is made. This paragraph should not apply to Alka-Seltzer. It fails to differentiate aspirin from a buffered solution of sodium acetylsalicylate. The underlined portion is only appropriate to the degree that it relates to a solid mixture of an antacid and aspirin in its acid form intended to be taken as such. It does not appropriately apply at all (for reasons already stated and supported by data submitted to the Panel) in referring to a reaction mixture containing the water soluble wholly dissolved sodium acetylsalicylate in a buffered solution.

EXHIBIT B

(Pages 45 and 46)

II. Conditions under which antacid products are not generally recognized as safe and effective or are misbranded.

The use of antacids under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Panel concludes that the ingredients, labeling, and combination drugs involved should be removed from the market until scientific testing supports their use.

A. *Active ingredients*

No active ingredient for which (handwritten note not legible) not included in Category I or Category III has, in the Panel's opinion, been shown by adequate and reliable scientific evidence to be safe and effective.

B. *Labeling*

The Panel concludes that it is not truthful and accurate to make claims or to use indications on the package label that the product may directly affect "nervous or emotional disturbances", "excessive smoking", "food intolerance", consumption of "alcoholic beverages", "acidosis", "nervous tension headaches", "cold symptoms", and "morning sickness of pregnancy" since the relationship of such phenomena to gastric acidity is both unproven and unlikely.

EXHIBIT C

C. *Drugs combining antacid and other active ingredients*

1. *Although the Panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for concurrent symptoms, it concludes that fixed antacid-aspirin combinations are irrational for antacid use alone and therefore should not be labeled or marketed for such use. Not only are OTC antacids-sometimes indiscriminately used, which may lead to aspirin toxicity with such combinations, but aspirin also has a potential for damaging the gastrointestinal mucosa by the topical action of breaking the mucosal barrier or by other mechanisms.*[1]

CITATIONS

1. Brodie, DA and Chase, BJ; "Role of Gastric Acid In Aspirin-Induced Gastric Irritation In The Rat", Gastroenterology, *53*:604–610, 1967.

2. Grossman, MI; Matsumoto, KK; Lichter, RJ; "Fecal Blood Loss Produced By Oral and Intravenous Administration of Various Salicylates", Gastroenterology, *40*:383–388, 1961.

3. *Jennings, GH; "Alka Seltzer and Haematemesis", Letter to the Editor; Brit. Med. J., 16:475, 1965.*

NOTE.—Delete *Jennings citation*. See memorandum comment.[2][3]

2. The Panel concludes that it is not safe and effective concurrent therapy to add an anticholinergic ingredient to an OTC antacid product, because optimal use of antacids and * * *.

Attached is a certified copy of page 43 of the Panel Report submitted by Miles Laboratory on December 29, 1972. The changes shown on the certified copy were made in red in the original document submitted by Miles Laboratory. A certified copy is submitted since the red markings on the Miles submission could not be reproduced.

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[1] Blue ink underlined portions appear in italic.

[2] In the original submission, Miles Laboratories' "Notes" appear in the left hand margins next to the pertinent portions of the draft report.

[3] At this "Note" there is a handwritten arrow with the word "out" pointed to the Jennings citation (3).

(Page 43)

NOTE.—The first two paragraphs in Section I.D. have been rewritten in order more clearly to illustrate the insertions which are suggested to be made therein and which are underlined in blue ink.[1] These insertions replace the phrase "a corrective for an antacid side effect" and are necessary in order for these paragraphs to conform to the language contained in page 50.

D. *Drugs combining antacid and other active ingredients*

The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor *a corrective for an antacid side effect,* will contribute to the product's safety and effectiveness for use in antacid therapy alone. The addition of non-antacid or non-corrective ingredients may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be allowed, the use of the combination of an antacid and an active ingredient that is neither an antacid nor *a corrective for an antacid side effect* should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and non-antacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require the relief of both of the active ingredients. The dual indication should clearly be stated on the label [and the label should include a prominently displayed warning that such a combination shall not be used for the treatment of heartburn and or indigestion and or sour stomach unless these symptoms are accompanied by indications for an analgesic.][2] Such a product is not appropriate for peptic ulcer and related * * *.

NOTE.—The use of Alka-Seltzer for upset stomach and symptoms which indicate the use of an analgesic is safe and effective. No such warning is appropriate.[3]

Certified to be a true copy of the original.

HENRY DAUSCH.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
OFFICE OF THE SECRETARY,
May 8, 1975.

Memorandum to: Peter Barton Hutt (GCF–1).
From: Gary Yingling (GCF–1).
Subject: Fountain Committee Hearing.

Gil Goldhammer has asked about a certain document which we received from Miles Laboratory which suggests that changes be made in the December 22, 1972 antacid draft. The following is a chronology of events that I believe occurred prior to and after receipt of the memorandum from Miles.

1. The panel asked prior to their September meeting that the minutes from the prior meetings be put together in a report form. This was done and appears as as undated draft. Number 13 of the draft states "that fixed antacid-aspirin combinations should not be labeled or marketed for their antacid effects."

2. The panel met on September 7, 8 and 9, 1972.

3. The minutes from the meeting of September 7, 8 and 9 indicate that it was the panel's position that a fixed antacid-analgestic combination should not be labeled or marketed for their antacid effect.

4. A redraft of the undated report was prepared for the panel and dated November 11, 1972. It was sent to them on that date. On page 50, the panel stated that the combination of antacids and analgesics should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both an antacid and analgesic. This dual indication should be clearly stated In the product label together with a warning against use for longer than 3 days except under the advice and supervision of a physician.

5. On December 1, 1972 Gary Yingling sent a letter to Franz Ingelfinger commenting on the November 11 draft report. He pointed out areas that had not been dealt with and provided additional references.

6. The panel met on December 8 and 9, 1972. Miles Labortory made a presentation to the panel on that date.

[1] Blue ink underlined portions in the original appear in italic.
[2] Bracketed material indicates portions crossed out in Miles Laboratories' submission.
[3] In the original submission, Miles Laboratories' "Notes" appear in the left hand margins next to the pertinent portions of the draft report.

7. The minutes from the December 8 and 9 panel meeting state on page 6 that it is rational to combine an antacid with an analgesic if the individual who uses the product concurrently has symptoms which require for their relief the pharmacologic action of both an antacid and an analgesic. The dual indication should clearly be stated on the label and should include a prominently displayed warning that such a combination shall not be used for the treatment of heartburn and/or indigestion and/or sour stomach unless these symptoms are accompanied by an indication for an analgesic.

8. On December 22, 1972 the OTC Staff mailed a final proposed draft report of the Advisory Review Panel on OTC antacid drugs to the panel members and liaisons. Page 43 of that report had the same language as the meeting minutes of December 8 and 9, 1972.

9. On January 3, 1973 Armond Welch sent a memorandum to the panel stating that paragraph 1 on page 43 had been redrafted. The proposed revision had been discussed with Dr. Ingelfinger and would be included as an agenda item of the conference call on January 9.

10. The revision dated January 3, 1973 states that "the indication section of the labeling should state clearly that the combination should be used only when heartburn and/or acid indigestion and/or sour stomach are accompanied by indications for an analgesic.

11. On January 5, 1973 Armond Welch sent a memorandum to the panel concerning the conference call and reminded them that revision of page 43 dated January 3, 1973 had been distributed.

12. Dr. Mark Novitch's calendar shows that a meeting was held with Adrien Ringuette and Charles Jolly of Miles Laboratory on January 5, 1973. The calendar indicates that Mr. Hutt was in attendance; no reference appeared as to Mr. Yingling, Director of OTC Review. Mr. Yingling believes that he was at the January 5 meeting and received from representatives of Miles at that time a volume entitled, *Memorandum, December 29, 1972.* The written statement, "given to me personally, GLY" appears on the front of that document. Handwritten notes and doodles by Mark Novitch also appear in the volume.

13. In the Miles document dated December 29, 1972 is (1) a January 3, 1973 memorandum entitled "Notes for Presentation by the Commissioner to Dr. Ingelfinger, (2) a December 29, 1972 memorandum which is 10 pages in length and has the name, Adrien L. Ringuette on the last page. Attached to the ten page memorandum is Appendix A through D. Appendix A is the December 22, 1972 antacid panel draft report with red underlining and proposed addition done by Miles Laboratory.

14. The volume was filed by Gary Yingling in the OTC Administrative File [1] sometime after the antacid panel completed its review. Mr. Yingling assumed that it was an educational volume prepared by Miles for the OTC Staff as to issues that need resolution. It was never distributed to or discussed with the panel and therefore was not placed in the Hearing Clerk's office.

15. On January 8, 1973 Armond Welch, Executive Secretary, called Dr. Ingelfinger and told him that in addition to page 43 the revision on page 22 and 46 had also been sent. Dr. Ingelfinger had proposed a change on page 22 and Dr. Grossman proposed a change on page 46.

16. The panel had a telephone conference call on January 9, 1973.

17. The summary minutes of the telephone conference call states that changes were made concerning the antacid-analgesic combination on page 43.

18. On January 12, 1973 Armond Welch sent a draft including all the changes that were proposed during the conference call on Tuesday, January 9, 1973.

19. January 23, 1973 Franz Ingelfinger signed the final report as the panel chairman.

20. On January 30, 1973 Armond Welch sent a copy of the final report signed by Dr. Ingelfinger to all of the panel members.

Attached is a copy of the *Federal Register* document of June 4, 1974, which sets forth the effective dates for the final order for antacid and antiflatulent products generally recognized as safe and effective and not misbranded.

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[1] EDITOR'S NOTE.—The administrative file referred to is evidently not the same as the administrative record referred to in hearing discussion at p. 201.)

[From the Federal Register, June 4, 1974]

RULES AND REGULATIONS

PART 332—ANTIFLATULENT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—[Reserved]

Subpart D—Labeling

SUBPART A—GENERAL PROVISIONS

§ 332.1 Scope.

An over-the-counter antiflatulent product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

SUBPART B—ACTIVE INGREDIENTS

§ 332.10 Antiflatulent active ingredients.

Simethicone; maximum daily dose 500 mg. There is no dosage limitation at this time for professional labeling.

§ 332.15 Combination with non-antiflatulent active ingredients.

An antiflatulent may contain any generally recognized as safe and effective antacid ingredient(s) if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

SUBPART C—[RESERVED]

SUBPART D—LABELING

§ 332.30 Labeling of antiflatulent products.

(a) *Indications.* The labeling of the product represents or suggests the product as an "antiflatulent" and/or "to alleviate or relieve the symptoms of gas."

(b) *Direction for use.* The labeling of the product contains the recommended dosage per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age groups if appropriate, followed by "except under the advice and supervision of a physician." The words "or as needed" may be used after the recommended dosage per time interval or time period.

§ 332.31 Professional labeling.

(a) The labeling of the product provided to health professionals (but not to the general public) may contain as additional indications postoperative gas pain or for use in endoscopic examination.

(b) Professional labeling for an antiflatulent-antacid combination may contain information allowed for health professionals for antacids and antiflatulents.

Effective date. This order shall become effective on July 5, 1974, except that all labeling for products not receiving an extension of the effective date for reformulation shall become effective on June 4, 1975, and where reformulation is necessary and an extension is granted shall become effective on June 4, 1976. The labeling of a product to health professionals shall after June 4, 1976, contain the neutralizing capacity of the product as calculated using the procedure set forth in § 331.26.

Dated: May 29, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.74-12666 Filed 6-3-74;8:45 am]

As stated in the hearing, the note to the editor by G. H. Jennings which appeared in the February 16, 1963 *British Medical Journal* was deleted from the references and the article by G. H. Jennings "Causal Influences in Haematemesis and Melaena" was substituted for it. This was done for two reasons: 1. a complete scientific article provides a more sound basis for scientific decisionmaking; 2. the information included in the *Gut* article published in 1965 provides new and additional information beyond that conveyed in the note to the editor which appeared in 1963.

[From the British Medical Journal, Jan. 26, 1963]

"ALKA-SELTZER" AND HAEMATEMESIS

SIR,—Your report in the October 6 issue of the *Journal* (p. 916) on the Symposium on Salicylates sponsored by the Empire Rheumatism Council referred to gastro-intestinal bleeding due to aspirin and stated, "soluble formulations were no safer than plain aspirin." Although this statement might be true for some soluble formulations, it is not true for all of them.

Actually, data presented at the symposium as well as the published observations of three groups of investigators [1-3] indicate a marked reduction in the bleeding with the use of buffered effervescent preparation ("alka-seltzer"). This preparation must be dissolved in water prior to ingestion. Other soluble salicylates such as calcium aspirin and choline salicylate [4 5] and sodium salicylate [6] also lead to less bleeding.—I am, etc.,

CLARKE DAVISON,
Department of Pharmacology,
George Washington University School of Medicine,
Washington 5, D.C., U.S.A.

REFERENCES

[1] Wood, P. H. N., Harvey-Smith, E. A., and Dixon, A. St. J., *Brit. med. J.*, 1962, 1, 669.
[2] Stubbé, L. Th. F. L. Pietersen, J. H., and van Heulen, C., *ibid.*, 1962, 1, 675.
[3] Leonards, J. R., *Fed. Proc.*, 1962, 21, 452.
[4] Muir, A., and Cossar, I. A., *Amer. J. dig. Dis.*, 1961, 6, 1115.
[5] Pierson R. N., jun., Holt, P. R., Watson, R. M., and Keating, R. P., *Amer. J. Med.*, 1961, 31, 259.
[6] Winkleman, E. I., and Summerskill, W. H., *Gastroenterology*, 1961, 40, 56.

SIR,—Within the past six weeks I have attended two cases of severe haematemesis occurring with a few hours of taking "alka-seltzer" tablets. Alka-seltzer consists of aspirin plus buffering and effervescent agents, but advocates itself both on television and on the container for "stomach upsets."

In view of the generally accepted relationship between the taking of aspirin in any form and gastro-intestinal haemorrhage, is it not time that measures were taken to prevent the wide advertising of a product for dyspeptic symptoms to dyspeptic patients for whom it is potentially dangerous?—I am, etc.,

A. C. ARTHUR,
Stoke-on-Trent, Staffs.

[From the British Medical Journal, Feb. 16, 1963]

"ALKA-SELTZER" AND HAEMATEMESIS

SIR,—May I support Dr. A. C. Arthur's views on "alka-seltzer" tablets (January 26, p. 260) as a cause of bleeding from the stomach. I have recently been reviewing my cases of gastro-intestinal bleeding and I find that in just over two years, from the end of 1958, I saw 134 such cases due to aspirin-containing preparations. Of these, twenty-four subjects had very recently taken alka-seltzer and nineteen had not taken any other salicylate except alka-seltzer, which had often been taken in small doses of one or two tablets.

The advertisement of such tablets as giving relief from stomach upsets is in my opinion morally wrong, since it is in subjects of these disorders that aspirin is most prone to cause haemorrhage. If such advertising cannot be prevented then at least the fact that the advertised tablets contain aspirin should be made evident to all. Most of my patients were ignorant of this fact.

The trade names of many aspirin-containing preparations: "anadin," "antoin," "Beecham's powders," "maeprin" and "solprin," to name only a few, do not reveal to the uninitiated their aspirin content. All these preparations feature in the immediate antecedent history of haematemesis in my list of cases.—I am, etc.,

G. H. JENNINGS.
Edgware General Hospital, Edgware, Middlesex.

SIR,—Dr. A. C. Arthur recently reported (January 26, p. 260) two cases of haematemesis following the ingestion of "alka-seltzer" tablets. I have just attended a man with a chronic duodenal ulcer who had a severe haematemesis and melaena shortly after taking five tablets of alka-seltzer. I agree with Dr. Arthur that measures should be taken against the advertisement of these aspirin-containing tablets for dyspeptic symptoms.—I am, etc.,

MALCOLM M. SEGALL.
The Royal Hospital, Sheffield.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., September 2, 1975.

Hon. L. H. FOUNTAIN,
Chairman, Subcommittee on Intergovernmental Relations and Human Resources, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: During the hearing on the over-the-counter (OTC) drug review, questions were raised about the manner in which the Antacid Panel reached its decision on drug products containing antacid and analgesic ingredients. I pointed out at that time that I was fully responsible for the final decision on this matter. In order to make the record complete, I am requesting that this letter be inserted in the printed record at the point in the discussion where this matter was raised.

The Subcommittee on Monopoly of the Senate Select Committee on Small Business held a hearing on this precise issue during June 1973, after the Antacid Panel had issued its report and Commissioner Edwards had published it in the Federal Register as a proposal, but before I had reviewed it and issued the tentative final monograph. At that hearing, evidence was presented in opposition to the combination of antacid and analgesic ingredients. In order to be as fair as possible, the Food and Drug Administration (FDA) included the transcript of that Subcommittee hearing as part of the comments on the proposed monograph. Each point made in that hearing was dealt with fully in the preamble to the tentative final order.

Similarly, additional information was brought forward by the Health Research Group at the time of my public hearing on the tentative final order. Even though it was improper to introduce new evidence not already included in the administrative record at that time, I nonetheless opened the record for that purpose and, in the preamble to the final monograph, dealt with all of the information provided.

Thus, in two instances, the Food and Drug Administration went out of its way to permit the introduction of additional information beyond the time it should already have been provided the Antacid Panel. We considered the additional material in detail and dealt with it in detail as part of the administrative process. I know of no scientific or medical information that was ignored or not dealt with fully in this manner.

Ms. Annette Dickinson, the consumer liaison member of the Antacid Panel chosen by the consortium of consumer organizations, submitted comments to the Hearing Clerk dated June 4, 1973, which commented upon this specific matter. A copy is included for the printed record. As she pointed out, although she is not sure whether the right decision was made, some of the panel members had felt strongly from the very beginning that combination OTC drug products containing antacid and analgesic ingredients are rational. She therefore wrote "to defend the integrity with which I believe the Panel arrived at" its decision on that matter.

After the final monograph was promulgated, the Senate Subcommittee again held a public hearing to consider the matter in June 1974. I had made the final decision on the monograph, and I defended that decision on medical and scientific grounds and stated that a contrary conclusion would not have been warranted by all of the information available. There is no information that has since been brought to my attention that would lead to a contrary conclusion today.

Accordingly, it is apparent that, from a scientific and medical standpoint, the conclusion reached by the panel and by me remains entirely valid.

Sincerely yours,

ALEXANDER M. SCHMIDT, M.D.,
Commissioner of Food and Drugs.

Enclosure.

SILVER SPRING, MD., *June 4, 1973.*

MS. BERYL MCCULLAR,
Hearing Clerk, Food and Drug Administration,
Rockville, Md.

DEAR MS. MCCULLAR: Comments on the proposed monograph for OTC Antacid Products will be submitted separately by several consumer organizations. I concur with the comments submitted by the Consumer Federation of America, but as the Consumer Liaison member of the Antacid Panel, I submit the following additional remarks.

I commend the FDA for undertaking this broad review of all OTC products. Even given the fact that each panel member will bring certain biases to the deliberations, this review should result in an overall improvement in the efficacy and safety of OTC drugs. Fault will certainly be found with the specific findings of any single expert panel. Nevertheless, it seems clear that there are some ingredients now being widely used in OTC products which are unquestionably either unsafe or ineffective. Even if the sole net result of the review is to remove such ingredients from these drugs, that will be a significant and long overdue accomplishment.

I believe that the individuals who made up the Antacid Panel worked very earnestly at this review. They made a number of recommendations which I believe can be applauded from a consumer standpoint:

Taking a generally strong stand against fixed combination products;

Eliminating ingredients (category II) which are clearly unsafe or ineffective and label claims which are clearly inappropriate;

Requiring industry to conduct further testing of ingredients of doubtful effectiveness and to provide support for doubtful product claims (category III);

Requiring that the label clearly state the quantitative composition of active ingredients in the product;

Requiring that any product labeled "antacid" have at least a certain minimum neutralizing capacity;

Requiring warnings on labels to inform consumers which products should be avoided by persons with kidney disease and which products may cause constipation or diarrhea in some persons; and

Requiring that the sodium content be stated on the label.

Any review panel with powers as broad as those of the OTC Review Panels is forced to walk a precarious line. On the one hand they wish to be tough on the products they consider, in order to protect the consumer to the best of their ability and to avoid charges of "giving in" to industry pressures. On the other hand, they want to avoid being arbitrary, in order to avoid eliminating products which are in fact useful. I believe the antacid panel made every effort to give the FDA their best expert advice, without being unnecessarily arbitrary and without being consciously lenient.

The panel has nevertheless been accused of leniency in one instance, which I wish to discuss briefly. The panel had a charge to determine whether fixed combination products provide "rational concurrent therapy for a significant proportion of the target population." In general, the Antacid Panel took a very hard line against combinations—they specifically prohibited combinations of antacids with anticholinergics, sedatives, laxatives, anti-peptic ingredients, proteolytic agents, bile salts, or anti-emetics. In addition, the panel firmly stated that products sold solely as antacids (non-combination products) may not contain aspirin. Yet in spite of their strong stand against most combinations and against aspirin in antacid products, they classified one fixed combination product—the analgesic/antacid combination—as GRAS and GRAE (generally recognized as safe and generally recognized as effective). The major product allowed by this decision is Alka-Seltzer, manufactured by Miles Labs; the analgesic ingredient in Alka-Seltzer is aspirin. The fact that this is virtually the only combination allowed under the monograph has led to charges that the panel gave in to Miles under pressure. Actually, however, some of the expert panel members felt strongly from the very beginning that "a significant proportion of the target population" does in fact have headache and acid indigestion at the same time, and that as long as the label clearly stated that the product was to be used only by people with concurrent symptoms, there was no justification for banning the combination. The panel eventually adopted that position. I am not sure whether that made the right decision—the Health Research Group will argue strongly that they did not—but I believe that the more reluctant members of the panel agreed to this

decision because of their colleagues' strong convictions, not because of pressure or persuasion from Miles. My purpose here is not to support the decision—but merely to defend the integrity with which I believe the panel arrived at it. It is almost certainly true that many consumers are now taking Alka-Seltzer and similar products as antacids, rather than using the products as true combination drugs. Those consumers will need education about the proper use of such products; if the appearance of the package is otherwise unchanged, the new indications for use could go un-noticed for some time. It is my hope that a consumer education campaign will be forthcoming from consumer organizations and from the FDA, alerting the purchaser to the changed label indications for this combination product.

The panel made two labeling decisions with which I take exception. First, the panel decided that the neutralizing capacity of an antacid should be stated in ethical labeling (for doctors) but not on the consumer label. They feel that the product with the highest neutralizing power may not be the most desirable product for the consumer. I sympathize with this dilemma, since the consumer comparing labels probably would assume that extra neutralizing power means a better product. However, I feel that the consumer has the right to all the available information about any product in the marketplace, and I wish the panel had devised some way to provide this information in a way that would not mislead the consumer about the worth of the product. Moreover, the monograph does not specifically prohibit the manufacturer from stating the neutralizing capacity on the label, and the FDA does not have direct jurisdiction over advertising claims for OTC drugs. I feel certain that some manufacturers will take advantage of this to make claims for the superior neutralizing power of their product. If that happens, the consumer should be able to look on the label to verify the neutralizing capacity for himself and to compare it with other products.

Second, the panel recognized that aluminum compounds interfere with tetracycline absorption and may interfere with other prescription drugs. Other antacid ingredients may also interfere with the absorption of prescription drugs; but because of conflicting evidence, the panel decided not to require a label warning of this possible interference. This leaves the matter entirely up to the doctor writing the tetracycline prescription, who may not even be aware that his patient is taking antacids. I believe it would have been preferable to alert the consumer to the possibility of interference. A panel member once stated that we must educate consumers to the fact that they cannot combine drugs innocently; this could have been the beginning of such an education.

Another area in which I am personally very interested is the safety and usefulness of inactive ingredients used in antacids and in other OTC drugs as colorings, flavorings, excipients, binders, etc. The panel was charged only to review the active ingredients, but I am not satisfied that the safety of the inactive ingredients can be taken for granted. Nor am I confident that the safety of these ingredients is adequately monitored by the FDA. As a first step, I urge the FDA to seek and/or to exercise authority to require the labeling of inactive as well as active ingredients of OTC drugs. The consumer deserves to know all of the ingredients of any product which he or she purchases, in order that the purchase can be based on rational choice and not on chance. As long as ingredients are allowed to remain hidden from the public, the consumer runs the risk of consuming large amounts of substances which he would not knowingly purchase. Second, I urge the FDA to establish one more OTC panel—a panel to review the safety and usefulness of the inactive ingredients used in formulating antacids and all other OTC drugs which are being reviewed.

I am very pleased to have had the opportunity to serve as the Consumer Liaison member on this panel.

Sincerely,

ANNETTE DICKINSON.

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